NATIONAL OPEN UNIVERSITY OF NIGERIA

FACULTY OF HEALTH SCIENCES

COURSE CODE: NSC307

COURSE TITLE: CLINICAL PHARMACOLOGY AND CHEMOTHERAPY

COURSE GUIDE
NSC307
CLINICAL PHARMACOLOGY AND CHEMOTHERAPY

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Introduction

Pharmacology is the science of drugs. In a broad sense it deals with interaction of exogenously administered chemical molecules (drugs) with the living systems. It encompasses all aspects of knowledge about drugs. When we talk about clinical pharmacology it deals with effective and safe use of medicinal substances in the clinics and hospital settings. This can be extended to safe self-medication. For thousands of years most drugs were crude natural products of unknown composition and limited efficacy. Over the past 100 years, drugs have been purified chemically, characterized and a vast variety of highly potent and selective new drugs have been developed. The mechanism of action including molecular target of many drugs has been elucidated. This has been possible due to prolific growth of pharmacology which forms the backbone of rational therapeutics. The two main divisions of pharmacology are pharmacodynamics and pharmacokinetics. Clinical pharmacology can best be defined as the science of substances used to prevent, diagnose, and treat diseases. The science of drug preparation and the medical use of drugs began to develop as the precursor to pharmacology.

Learning Expectations

This course guides you briefly on what to expect from reading this material. The study of pharmacology is very important because it enables us to know the actions of drugs on the body and how various drugs are used for different ailments. About fifty years ago there began a major expansion of research efforts in all areas of biology. As new concepts and new techniques were introduced, information accumulated about drugs action and the biological substrate of that action, the receptor. The molecular mechanism of action of many drugs has now being identified and numerous receptors have been isolated, structurally characterized and cloned. Two general principles that the student should remember is that all substances under certain circumstances can be toxic and that all therapies promoted as health enhancing should meet the same standards of evidence of efficacy.

Course Aims

The aim of the course is simple - to provide an understanding and appreciation of pharmacology and chemotherapeutics. In addition, this course is set to achieve some objectives. After going through this course, you should know;

- Various definitions e.g. Clinical Pharmacology, Toxicology, Pharmacokinetics.

- Routes of drug administration, distribution and elimination.
- The basic pharmacology of cardiovascular drugs e.g., antihypertensives; Various antibiotics e.g., beta lactam antibiotics, the tetracyclines.
- About various parasitic infections and their drug treatment e.g. anti-malarias for malaria treatment.
- The differences between orthodox and traditional medicine.

Working through this Course

This course is intensive, requiring a great deal of time for reading and comprehension. It is with this in mind that the content was carefully developed to make it easily readable and readily comprehended. Yet, effort is still required on the part of the students comprehend and assimilate the course content. You should make yourself available for tutorials where you will meet your peers and can compare and transfer knowledge.

Course Materials

You will be provided with the following materials:

- Course Guide
- Study units

In addition, the course comes with a list of recommended textbooks which though are not compulsory for you to acquire or indeed read, but are necessary as supplements to the course material.

Study Units

The following are the study units contained in this course.

Module 1: Clinical Pharmacology and Pharmacokinetics

Unit 1 Introduction to Clinical Pharmacology and Chemotherapy
Unit 2 Dosage Forms
Unit 3 Pharmacokinetics and Routes of Drug Administration
Unit 4 Basic and Clinical Evaluation of New Drugs

Module 2: Interaction of Drugs with the Body Systems

Unit 1 Autonomic Nervous System
Unit 2 Drugs acting on the Respiratory System Including Anti-Asthmatic Drugs
Unit 3 Drugs acting on the Endocrine System including Anti-diabetic Drugs
Unit 4 Drugs used in Acid Peptic Disease

Module 3: Drugs Acting on the Cardiovascular System

Unit 1 Unit 2 Unit 3	Congestive Heart Failure and Drugs Used Cardiac Arrhythmia and Drugs Used Angina Pectoris and Drugs Used Hypertension and Anti-hypertensive drugs

Module 4: Chemotherapeutic Drugs

Unit 1	Chloramphenicol and Tetracyclines as Antibiotics Sulphonamides, Trimethoprim and Quinolones as Antibiotics
Unit 2	Beta Lactam Antibiotics and Other Inhibitors of Cell wall Synthesis
Unit 3	Antiviral Agents
Unit 4	Antifungal Agents
Unit 5	Chemotherapy of Cancer

Module 5: Parasitic Infections

Unit 1	Chemotherapy of Malaria
Unit 2	Chemotherapy Helminthic Infections

Module 6: Traditional Medicine

Unit 1	Introduction into Traditional Medicine Practice Medicinal
Unit 2	Plants

Text Books and References

Most recent editions of these Books are recommended for further reading.

Bertram G. Katzung: *Basic and Clinical Pharmacology.*

K. D. Tripathi: *Essentials of Medical Pharmacology.*

C. N. Aguwa: *Therapeutic Basis of Clinical Pharmacy in the Tropics.*

Richard D. Howkind and Mary J. Mycek Lippioncott illustrated Review: Pharmacology, Third Edition.

Beyer K. H: Discovery, *Development and Delivery of New Drugs, SP Medteal and Scientific Books.*

Assessment
There are two components of assessment for this course. The Tutor Marked Assignment (TMA) and the end of course examination.

Tutor-Marked Assignment
The TMA is the continuous assessment component of your course. It accounts for 30% of the total score. You will be given 10 TMAs to answer. Five (5) of these must be answered before you are allowed to sit for the end of course examination. The TMAs would be given to you by your facilitator and returned after you have done the assignment.

Final Examination and Grading
This examination concludes the assessment for the course. It constitutes 70% of the whole course. You will be informed of the time for the examination. It may or may not coincide with the University Semester examination.

Summary
This course intends to provide you with some underlying knowledge of pharmacology and chemotherapy.

We wish you success in this course. In particular we hope that you will be able to appreciate the importance of pharmacology in health care delivery.

We hope you will enjoy the course.

Best wishes.

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MODULE 1 CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

UNIT 1 INTRODUCTION TO CLINICAL PHARMACOLOGY AND CHEMOTHERAPY

CONTENTS

1.0 INTRODUCTION

In the late 18th and early 19th centuries Francios Megende and Claude Bernard began to develop methods of experimental animal physiology and pharmacology. When new ideas and techniques were introduced, information was got about drug action and the biological substrate of that action which is the receptor.

2.0 OBJECTIVES

At the end of this unit the learner will;

- know the definition of clinical pharmacology, toxicology, drug, pharmacokinetics, pharmacodynamics and chemotherapy
- Understand the actions of drugs on various systems of the body and different dosage forms.
- Understand various routes of drug administration
- Be able to compare traditional medicine and orthodox medicine.

3.0 MAIN CONTENT

3.1 Definition of Clinical Pharmacology

Pharmacology is the study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes. Clinical Pharmacology is the science of substances used to prevent, diagnose and treat diseases. Pharmacology simply is the science of drugs.

Toxicology is the branch of Pharmacology, which deals with the undesirable effects of chemicals on living systems from individual cells to complex ecosystems.

It is the study of poisonous effect of drugs and other chemicals with emphasis on detection, prevention and treatment of poisoning.

3.2 Definition of Chemotherapy and Drug

Chemotherapy is the treatment of systemic infection / malignancy with specific drugs that have selective toxicity for the infecting organism / malignant cell with no or minimal effects on the host cells:

A drug is any substance that can bring about a change in biological function of the body through its chemical action. Drugs may exist in solid, liquid or gaseous form. Example of solid is paracetamol tablet and ampicillin

capsules. Examples of drugs in liquid form are propranolol and formaldehyde.

Drugs can thus be divided into pharmacodynamic agents and chemotherapeutic agents.

3.3 Definition Pharmacokinetics and Pharmacodynamics

Pharmacokinetics (movement) involves what the body does to the drug
Pharmacodynamics (power) involves what the drug does to the body.

3.4 Interaction of Drugs with Body Systems

Most of the time drug molecule interacts with a specific molecule in the biological system that plays a regulatory role. The molecule is termed a receptor. For a drug to interact chemically with its receptor, a drug molecule must have the appropriate size, electrical charge, shape and atomic composition. In addition, a drug is often administered at a place distant from its intended site of action e.g. pain tablet given orally to a patient to relieve headache. Therefore, a good drug must have the necessary properties to be transported from its route of administration to the site of action.

3.5 Dosage Form Design

What do we mean by dosage form? A dosage form is the form in which a drug substance can be administered to a patient. A tablet or syrup is a dosage form. Drugs are not usually administered as pure chemical substances but are almost always given in formulated preparations, which could range from relatively simple solution to complex drug delivery systems through the use of appropriate additives or excipients in order to provide varied and specialized pharmaceutical functions.

Different dosage forms are:

- Tablets
- Capsules
- Suspensions
- Solutions emulsions
- Suppositories
- Injections inhalers and
- Infusions.

- **Oral Dosage**

Advantages of Oral Administration

1. It is convenient to administer and does not need an expert.
2. It is not as expensive as injections to prepare
3. It is usually cheaper to administer than some other dosage forms like infusions

Disadvantages of Oral Dosage Form

1. Relatively slow onset of action
2. Possibilities of irregular absorption and destruction of certain drugs by enzymes and secretions of the GIT e.g. insulin products are inactivated by the action of stomach fluids.
3. Changes in drug solubility can result from reactions with other materials present in GIT e.g. interference of absorption of tetracycline through the formation of insoluble complexes with calcium which can be made available from food or formulation additives.
4. Gastric emptying time: Drugs are either weak acids or weak bases. Drugs which are weak acids will be largely unionized in the stomach and therefore will be more absorbed.

SELF ASSESSMENT EXERCISE 1

1. Define Clinical Pharmacology and Chemotherapy
   Clinical Pharmacology is.....
   Chemotherapy is.....

2. Name the various dosage forms and state the advantages and disadvantages of oral dosage forms

Various dosage forms:

a. .....
b. .....
c. .....
d. . .....
e. .. ..
f. .....
g. .....
h. .....
i. .....

Oral dosage advantages:

i .....
ii.....

iii.....

Oral dosage disadvantages:

i. ……

ii. …….

iv ……

3.6 Routes of Drugs Administration

Routes of drug administration are locations in which drugs are placed in order to get into the body.

Drugs can be in various dosage forms for convenient and efficacious treatment of a disease. Different dosage forms are designed to provide the drug in a suitable form for absorption from each selected route of administration.

Oral Route: Oral dosage forms are usually intended for systemic effects resulting from drug absorption through the various mucosa of the gastrointestinal tract.

Parenteral Route: The three main parenteral routes are subcutaneous, intramuscular, and intravenous. Other routes such as the intracardiac and intrathecal routes are less popular parenteral routes. Parenteral routes are preferred in emergency situations, when patients are unconscious or when they cannot swallow.

Topical Route: Drugs are applied topically i.e. on the skin, for local action. Drug absorption is primarily through sweat glands, hair follicles, sebaceous glands and through the stratum corneum.

Respiratory Route: The lung provides an excellent surface for absorption when the drug is delivered in gaseous or aerosol form. This is useful for the treatment of respiratory problems like asthma.

3.7 Traditional Medicine

Traditional medicine is defined by the World Health Organization (WHO) as the sum total of knowledge and practice, whether explicable or not, used in diagnosis, prevention and elimination of physical, mental and social imbalance and relying extensively on experience and observation handed down from generation to generation, whether verbally or written. This includes definitions of various types, acupuncture and various types of scarifications, osteopathy, and hydropathy, aromatherapy and of

course, treatment with preparations from plants.

Differences between Traditional Medicine and Orthodox Medicine

1. Traditional medicine is not well regulated by government while orthodox medicine is well regulated.
2. Traditional medicine is closer to the people while orthodox medicine is not as close to the people
3. Traditional medicine is usually cheaper than orthodox medicine.
4. Traditional medicine practitioners sometimes make some mistakes which is uncommon in orthodox medicine.
5. The practice orthodox medicine requires stringent academic qualifications. This is not the case with traditional medicine.
6. Dosage of drugs in orthodox medicine is well regulated and measured before administration. Dosing is rarely standardized in traditional medicine

SELF ASSESSMENT EXERCISE 2

1. What do you understand by traditional medicine and orthodox Medicine?
   Traditional Medicine is.....
   .....

   Orthodox Medicine is.....

Difference between traditional medicine and orthodox medicine,

a

b

c.

d

e

f.

4.0 CONCLUSION

It is important to know the definition of clinical pharmacology, chemotherapy, toxicology, traditional and orthodox Medicine. It is also important to know what receptors are, routes of drug administration and the action of drugs on the systems of the body.

5.0 SUMMARY

You have learnt key things about interaction of drugs with body systems, dosage form design, routes of drug administration and definitions of clinical pharmacology, chemotherapy, drug, traditional medicine and its comparison to orthodox medicine.

ANSWER TO SELF ASSESSMENT EXERCISE 1

Clinical pharmacology is the science of drugs used to prevent, diagnose and treat diseases.
Chemotherapy is the treatment of systematic infection/malignancy with specific drugs that have toxicity for the organism/malignant cell with no/minimal effect in the host cells.
Various dosage forms are tablets, capsules, suspensions, emulsions, suppositories, injections, inhaler, and infusions.

Oral Dosage: Advantages

1. It is convenient to administer and does not need an expert
2. It is not as expensive as injections to prepare

It is usually cheaper than some other dosage forms like infusions

Oral Dosage: Disadvantages

1. Relatively slow onset of action
2. Possibilities of irregular absorption and destruction of certain drugs by enzymes and secretions of the GIT e.g. insulin products are inactivated by the action of stomach fluids.
3. Changes in drug solubility can result from reactions with other materials present in GIT e.g. interference of absorption of tetracycline through the formation of insoluble complexes with calcium which can be made available from food or formulation additives.
4. Gastric emptying time: Drugs are either weak acids or weak bases.

Drugs which are weak acids will be largely unionized in the stomach and therefore will be more absorbed.

ANSWER TO SELF ASSESSMENT EXERCISE 2

Traditional medicine is sum total of knowledge and practice, whether explicable or not, used in diagnosis, prevention and elimination of physical, mental and social imbalance and relying extensively on experience and observation handed down from generation to generation, whether verbally or written. Modem medicine deals with the newest medicine design, which involves the use of modem doctors, nurses and pharmacist in the diagnosis of ailment, dispensing of drugs and treatment of illness.

Refer to page 5 for the differences between traditional medicine and orthodox medicine

6.0 TUTOR-MARKED ASSIGNMENT

Name the various dosage forms and state the advantages of oral dosage form.

7.0 REFERENCES/FURTHER READINGS

K.D. Tripathi. Essential of Medical Pharmacology 8th Edition. 2019.

WHO global report on Traditional and Complementary Medicine 2019.

UNIT 2 DIFFERENT DOSAGE FORMS

CONTENTS

1.0 INTRODUCTION

In the last unit you were taught the definition of various terms like pharmacology, pharmacokinetics and chemotherapy. Here, you will learn about various dosage forms. The nature of the disease or illness against which the drug is intended is an important factor in selecting the type of dosage forms to be prepared. Factors such as the need for systematic or local therapy, duration of action and whether the drug will be used in emergency situations need to be considered too. A single drug substance may be prepared into a number of dosage forms to satisfy both the particular preference of the patient or physician and the specific needs of certain situations.

2.0 OBJECTIVES

At the end of the unit, the learner will be able to:

- define drug, dosage forms, and chemical names
- know what essential drugs are
- describe various dosage forms and give examples.

3.0 MAIN CONTENT

3.1 Definition of Drug

A DRUG is the single active chemical entity present in a medicine that is used for diagnosis, prevention, treatment/cure of a disease. This disease-

oriented definition of drug does not include contraceptive, or drugs used for health promotion. WHO (1966) gave a more comprehensive definition of drug as "Any substance or product that is used or is intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient".

3.2 Definition of Dosage Form

A dosage form: is the form of presentation of a particular medicine before it is administered for the treatment of a particular ailment.

Drug Nomenclature
A drug generally has three categories of names.

Chemical Name e.g. 1 -(Isopropylamino-3-(1 - naphthyloxy propan- 2-01 (Propranolol). This is cumbersome and not suitable for use in prescribing.

A code name e.g. RO i5 – 1788 (later named flumazenil) may be assigned by the manufacturer for convenience and simplicity before an approved name is coined.

Non-Proprietary Name

This is the name accepted by a competent body such as the United States, Adopted Name (USAN) council. The non-proprietary names of newer drugs are kept uniform by an agreement to use the recommended International Nonproprietary Name (-INN) only. But many older drugs have more than one non-proprietary name e.g. meperidine (USA) and pethidine UK, for the same drug until the drug is included in a pharmacopoeia. The nonproprietary name may also be called the approved name. When included in the official publication it is called official name.

Proprietary (Brand) Name

It is the name assigned by the manufacturer(s) to the drug. This is his property or trademark. This name often has a trademark symbol ® attached to it It is very common for a single drug to have more than one proprietary name.

Atenolol is also called Altol®, Atcardel®, Atecor®, Aten®, Betacard®, Lonul®, Teriolol®, and Tenormin® by different companies. Brand names generally differ in different countries e.g. timolol maleate eye drops are marketed as timoptic® in USA but as Glucomol® in India. Even the same

manufacturers may market the same drug under different brand names in different countries.

3.3 Essential Drug Concept

WHO defined essential drugs as those drugs that satisfy the priority health care needs of the population? They are selected with due regard to public health relevance, evidence of efficacy and safety, and comparative cost effectiveness. Essential medicines are intended to be available in the functioning health systems at all times and in adequate amounts. Those drugs that can meet the health care needs of the majority of the people in any country which are tested and not expensive should be considered by Government as Essential drugs.

Below are WHO criteria for a drug to be considered as Essential drug.

1. Adequate data on its efficacy and safety should be available from clinical studies.
2. It should be available in a form in which quality, including bioavailability, and stability in storage can be assured
3. Its choice should depend upon pattern of prevalent diseases, availability of facilities and trained personnel, financial resources, genetic, demographic and environmental factors.
4. When there are two or more similar drugs, choice should be made on the basis of their relative efficacy, safety, quality, price and availability. Cost - benefit ratio should be a major consideration.
5. Choice may also be influenced by comparative pharmacokinetic properties and local facilities for manufacture and storage.
6. Most essential drugs should be single compounds. Fixed ratio combination products should be included only when dosage of each ingredient meets the requirements of a defined population group, and when the combination has a proven advantage.
7. Selection of essential drugs should be a continuous process which should take into account the changing priorities for public health action, epidemiological conditions as well as availability of better drugs / formulations and progress in pharmacological knowledge.

3.4 Different Dosage Form

Different dosage forms are Tablets, Capsules, Suspensions, Solutions, Emulsions, Inhalers, Injections, Ointments and Creams

a. **Tablets.** Tablets are prepared by compression and contain drugs and formulation additives which are included for specific functions.

Tablets are solid single dosage forms which comprise medicaments, usually with excipients, compressed or molded into circular shapes, with flat or convex faces or other suitable shapes Tablets may be coated either to provide a protective coat from environmental factors for drug stability purposes or to mask unpleasant drug taste, as well as to protect drugs from the acid conditions of the stomach. Specialized tablet formulations are also available to provide controlled drugs release systems through the use of tablet. Core material / or polymeric coating membranes e.g. paracetamol tablet.

b. **Capsules -** Capsules are solid dosage forms containing drug and (usually appropriate) fillers enclosed in a hard or soft shell composed of gelatin e.g. Ampicillin capsules. A capsule is a dose of one or more medicinal substances enclosed in a hard or soft (flexible) gelatin shell.

c. **Suspensions -** They contain finely divided drugs suspended in a suitable vehicle and are a useful means of administering large amounts of drug which would be inconvenient if taken in tablet or capsule form e.g. flagyl® suspensions.

d. **Solutions:** are liquid preparations containing one or more soluble ingredients usually dissolved in water. Solutions include formulations such as elixirs and syrups. They are more absorbed than solid dosage forms or suspensions since drug dissolution is not required.

e. **Emulsions:** Emulsions are convenient preparations for the administration of unpalatable oils or oily solutions of drugs with unpleasant tastes.

f. **Suppositories:** They are solid unit dosage form intended for introduction into body cavities (usually rectal but also vaginal and urethral) where they melt, releasing the drug. Vaginal suppository is more appropriately called a pessary. The choice of suppository base or drug carrier can greatly influence the degree and the rate of drug release. The dosage form is indicated for drugs that are inactivated when given orally or when the oral route is precluded e.g. when a patient is vomiting or unconscious. Drugs administered rectally also enter the systemic circulation without passing through the liver, an advantage for drugs, which are greatly inactivated by the liver following oral route absorption.

Disadvantages

1. It is not socially accepted by some patients
2. Absorption is often irregular and difficult to predict.

Injections: Injections are sterile solutions, suspensions or emulsions, which contain one or more medicaments in a suitable aqueous or oily vehicle. Injections are usually administered parentally through subcutaneous, intramuscular and intravenous routes. Other less popular routes of injection are intracranial and intrathecal. Injections are preferred when absorption is essential as in emergency situations or when patients are unconscious or unable to accept oral medication.

Ointments and creams: These are usually applied topically for local actions. Drug absorption occurs through sweat glands, hair follicles, sebaceous gland and through the stratum corneum. Drugs applied to the skin for local effect include antiseptics, anti-fungals, anti-inflammatory agents, skin emollients. Examples of cream and ointments are canesten cream and sulphur ointment.

Syrups: Syrups are concentrated aqueous solutions of sucrose or other sugars to which medicaments or flavourings may be added. Glycerol sorbitol or other polyhydric alcohols are sometimes added in small amounts to medicated syrups to retard crystallization of sucrose or to increase solubility of other ingredients

SELF ASSESSMENT EXERCISE

a. Define a Drug b. What is an essential drug (criteria)

4.0 CONCLUSION

Drugs are in different dosage forms. The state of health of the patient and the routes of administration of the drug determine the dosage form that will be used.

5.0 SUMMARY

We have learnt about the definitions of drug, dosage forms, chemical name, nonproprietary names and proprietary names. We should

understand the meaning of essential drug concept, and different dosage forms.

ANSWER TO SELF ASSESSMENT EXERCISE

a. **A drug:** Is the single active chemical entity present in a medicine that is used for diagnosis, prevention, treatment/ cure of a disease.

b. **Essential Drug Concept:** WHO defined essential drugs as those drugs that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence of efficacy and safety, and comparative cost effectiveness. Essential medicines are intended to be available in the functioning health systems at all times and in adequate amounts. Government should consider those drugs that can meet the health care needs of the majority of the people in any country, which are tested and not expensive as Essential drugs.

Below are WHO criteria for a drug to be considered as Essential drug.

8. Adequate data on its efficacy and safety should be available from clinical studies.
9. It should be available in a form in which quality, including bioavailability, and stability in storage can be assured
10. Its choice should depend upon pattern of prevalent diseases, availability of facilities and trained personnel, financial resources, genetic, demographic and environmental factors.
11. When there are two or more similar drugs, choice should be made on the basis of their relative efficacy, safety, quality, price and availability. Cost - benefit ratio should be a major consideration.
12. Choice may also be influenced by comparative pharmacokinetic properties and local facilities for manufacture and storage.
13. Most essential drugs should be single compounds. Fixed ratio combination products should be included only when dosage of each ingredient meets the requirements of a defined population group, and when the combination has a proven advantage.
14. Selection of essential drugs should be a continuous process which should take into account the changing priorities for public health action, epidemiological conditions as well as availability of better drugs / formulations and progress in pharmacological knowledge.

6.0 TUTOR-MARKED ASSIGNMENT

What are the criteria for calling a drug an essential drug?

7.0 REFERENCES/FURTHER READINGS

Igwillo C.J. West African Post graduate College of Pharmacist's Lecture, 3.

KD Tripathi. Essentials of Medical Pharmacology 8th Edition, pages 1-71. 2019.

The Pharmaceutical Codex: Principles and Practice of Pharmaceutics. 12th Edition, 1994.

UNIT 3 PHARMACOKINETICS AND ROUTE OF DRUG ADMINISTRATION

CONTENTS

1.0 INTRODUCTION

The purpose of drug treatment is to prevent, cure, or control various disease states. In order to achieve this goal, enough drug doses must get to the target tissues so that therapeutic yet nontoxic levels are obtained. Pharmacokinetics looks at the movement of a drug over time through the body. The clinician must recognize that the speed of onset of drug action is controlled by four fundamental pathways of drug movement and modification in the body. The four fundamental pathways are absorption, distribution, metabolism and elimination.

2.0 OBJECTIVES

At the end of the unit the students should;

- acquaint themselves with the various routes of drug administration
- know what is meant by absorption, distribution, metabolism and elimination of drug
- be able to distinguish between bioavailability, bioequivalence and therapeutic equivalence
- Understand the concept of pharmacokinetics.

3.0 MAIN CONTENT

3.1 Routes of Drug Administration

The route of administration is determined primarily by the properties of the drug (for example, water or lipid solubility, ionization etc.) and also by the therapeutic objectives e.g. the desirability of a rapid onset of action or the need for long term administration or restriction to a local site). There are two major routes of drug administration; Enteral and Parenteral.

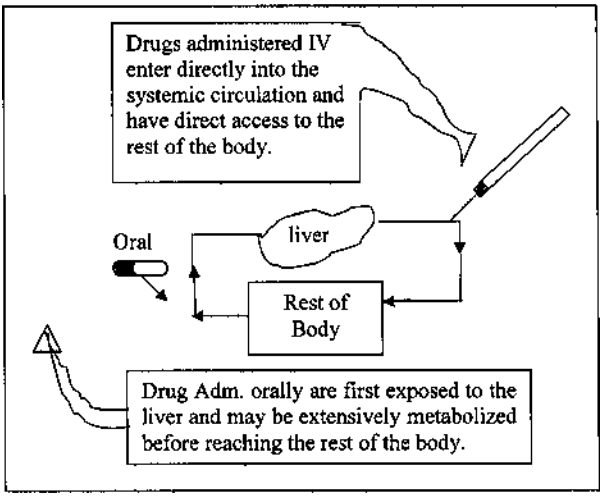
Enteral

Oral: Oral preparations are usually given by mouth. It is the most common route of drug administration. It is also the most variable. It involves the most complicated pathway to the tissues. Some drugs are absorbed from the stomach but the duodenum is the major site of entry into the systemic circulation because of its larger absorptive surface (Most drugs absorbed from the gastrointestinal (GI) tract enter the portal circulation and encounter the liver before they are distributed into the general circulation. (Figure3.1) First - pass metabolism by the intestine or liver limits the efficacy of many drugs when taken orally. The presence of food in the stomach delays gastric emptying so drugs that are destroyed by acid (e.g. Ampicillin Capsules) become unavailable for absorption. Enteric coating of a drug protects it from the acidic environment and may prevent gastric irritation.

Sublingual: This is the placing of a drug under the tongue which allows a drug to diffuse into the capillary network and to enter the systemic circulation directly. Drugs administered in this manner bypass the intestine and liver, and thus avoids first pass metabolism.

Rectal: Fifty percent of the drug administered by rectal route bypasses the portal circulation thereby making the drug more available. The sublingual and rectal routes of administration have the advantage that they prevent drug destruction by intestinal enzymes or by low pH in the stomach. The rectal route is also advantageous in cases when drug induces vomiting when given orally. The rectal route is usually used to administer drugs used in the cases of vomiting.

Figure 3.1
First pass metabolism can occur with orally administered drugs. IV = Intravenous



Source Lippincott's illustrated Reviews pharmacology, Third Edition by Richard .D. Howland Mary J. Mycek.

Parenteral: The three main parenteral routes are subcutaneous; intramuscular and intravenous. Other less popular routes are intracardiac and intrathecal. The parenteral route is preferred when absorption is essential as in emergency situations or when patients are unconscious or unable to accept oral medication and in cases when drugs are destroyed or poorly absorbed following oral administration.

Intravenous (I.V): I.V injection is the most common parenteral route. When drugs are administered intravenously, the drugs avoid the GI tract and first pass metabolism by the liver hence it is fully available in the body. Drugs given by IV route cannot be recalled by emesis or binding to charcoal, It is therefore important that sterility is maintained when giving IV injection to avoid cases of haemolysis or adverse drug reaction.

Intramuscular (I.M): I.M. is often a suspension of drug in a non-aqueous vehicle, such as polyethylene glycol. Absorption of drugs in aqueous solution is fast but that from depot preparation is slow.

Subcutaneous (SC): This route of administration is like I.M but it is slower than I.V route. It requires absorption. Example of drugs utilizing SC administration are silastic capsules containing levonorgestrel contraceptive that are implanted for long term activity.

Others: Other routes of drugs administration are inhalation, intranasal,

intrathecal / intraventricular.

Inhalation:- There is a rapid release of drug across the large surface of the mucous membranes of the respiratory tract and pulmonary epithelium, producing an effect like that of I.V injection e.g. ventolin inhaler.

Intranasal: Drugs are administered through the nose, e.g nasal decongestants

Intrathecal/ Intraventricular. Sometimes it is necessary to introduce drugs directly into the cerebrospinal fluid e.g. amphotericin used in treating cryptococcal meningitis.

Topical Route: Drugs are applied topically for local action. The route can also be used for systemic drug delivery but percutaneous absorption is generally poor and erratic e.g. clotrimazole is applied as a cream directly to the skin for the treatment of dermatophytosis.

Transdermal: This route of administration achieves systemic effects by application of drugs to the skin usually through a transdermal patch. The rates of absorption do vary depending on the physical characteristics of the skin at the site of application. Example of drug administered in this way is nitroglycerine used in the treatment of angina pectoris.

3.2 Absorption of Drugs

Absorption is the transfer of a drug from its site of administration to the bloodstream. In case of I.V administration, absorption is complete i.e. the total drug reaches the systemic circulation. However, in other routes, there is partial absorption, lowering bioavailability.

Transport of a Drug from the Gastro intestinal tract

Drugs may be absorbed from the GI tract by either passive diffusion or active transport.

Passive Diffusion: Drug moves from a region of high concentration to the one of lower concentration. It does not involve a carrier. It is not subject to carrier saturation. The process has a low structural specificity. Majority of drugs gain access to the body by this mechanism..

Active transport: depends on energy and it is driven by the hydrolysis of adenosine triphosphate. In this transport drug enters the body through specific carrier proteins that span the membrane. It is capable of moving drugs against a concentration gradient i.e., from a region of low drug

concentration to one of higher drug concentration.

Effect of PH on Drug Absorption

Most drugs are either weak acids or weak bases.
For Acidic drug,

$$HA \longrightarrow H^+ + A'$$

Acidic drug HA release a proton H^+, causing a charged anion (A') to form.

Weak Bases
In the case of weak bases, the protonated form of basic drugs is usually charged, and losses of a proton to produce the uncharged base (B):

$$BH^+ \longrightarrow B + H^+$$

Passage of an uncharged drug through a membrane
A drug passes through membranes more readily if it is uncharged. Thus for a weak acid, the uncharged HA can permeate through membranes, and A' cannot. For a weak base, the uncharged form B penetrates through the cell membrane but BH^+ does not.

To determine how much drug will be found on either side of a membrane, the relationship of pKa and the ratio of acid - base concentration to pH is expressed by the Henderson - Hasselbarch equation.

$$\text{pH} = pKa + \frac{Log\ [nonprotonated\ species]}{[protonated\ species]}$$

For Acids;

$$\text{pH} = pKa + \frac{Log\ [AI]}{[HA]}$$

For Bases;

$$\text{pH} = pKa + \frac{Log\ [B]}{[BH+]}$$

The lipid solubility of the non-ionized drug directly determines its rate of equilibration.

3.3 Physical factors influencing absorption.

Blood flow to the absorption site: The higher the blood flow to the absorption site the more the absorption that will take place at the site and vice versa. This is because there will be more drug where there is a higher blood flow.

Total surface area available for absorption: The greater the surface area of an organ the more the absorption of drug in the organ and vice versa. For example the intestine that has a surface area of about 1,000 fold greater than the stomach will have greater drug absorption than the stomach.

Contact Time at the absorption time: When a drug moves through a system like gastrointestinal tract quickly, e.g. when one has diarrhoea, it will not be well absorbed whereas the one that moves slowly, i.e. when there is no diarrhoea, will be more absorbed.

3.4 Bioavailability

Bioavailability is the fraction of administered drug that reaches the systemic circulation.

It is the rate and extent at which active agent of an administered drug passes into the systemic circulation. The usual method of determining bioavailability entails a pharmacokinetic study which involves measurement of drug levels in biological fluids obtained at various periods of time following administration of the drug.

3.4.1 Factors Affecting Bioavailability

1. Pathophysiological condition of the patient i.e. the sick nature of the patient.
2. Physicochemical properties of the drug
3. Dosage form of the drug.

3.5 Bioavailability Study

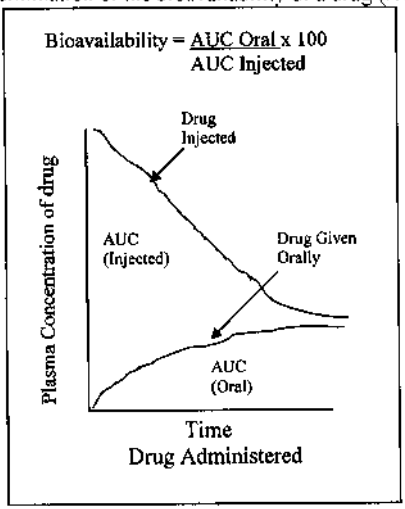
The usual method of determining bioavailability entails a pharmacokinetic study which involves measurement of drug levels in biological fluids obtained at various periods of time following administration of the drug. The commonly accepted biological fluid is blood (plasma or serum), although the use of urine levels has provided a non- invasive and acceptable method for some drugs. The absolute bioavailability or fraction of an extravascular dose available of the systemic circulation(f) is determined from the ratio of the area under the blood level (Saliva level) curve after extra vascular administration to that obtained after

intravenous administration.

F = (AUC)ev/(AUC)IV
F = Bioavailabity
AUC = Area under blood level curve
Ev = extra vascular
IV = Intravenous.

Figure 3.2

Determination of the bioavailability of a drug (AUC – Area under Curve).



Source
Lippincott's illustrated Reviews: Pharmacology, Third Edition, by Richard D Howkind and Nary J. Mycek.

3.6 Bioequivalence and Therapeutic Equivalence

Bioequivalence is a term generally applied to dosage forms of a drug that provide the same bioavailability regardless of the pharmaceutical composition of the dosage forms - Two related drugs are said to be bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations. Two similar drugs with a significant difference in bioavailability are said to be bioinequivalent.

Therapeutic equivalence or clinical equivalence refers to drugs which when administered in the same amounts will provide essentially the same therapeutic effect. Bioavailability study is quite useful in drug development, quality assurance and when comparisons are being made of

different dosage forms, different dose sizes, different dose regimen, different route of administration, different physical forms of the drug and different manufacturing processes.

3.7 Drug Distribution, Metabolism and Elimination

In order to achieve its effect, a drug must be administered at a site; it must be absorbed from the site and distributed through the body to its site of action. For the effect to wear off the drug must be metabolized and or excreted from the body.

Drug distribution is the process whereby a drug reversibly leaves the blood stream and enters the interstitium (extracellular) and / or the cells of the tissues. The delivery of a drug from the plasma to the interstitium primarily depends on blood flow, capillary permeability, the degree of binding of the drug to the plasma and tissue proteins and the relative hydrophobicity of the drug.

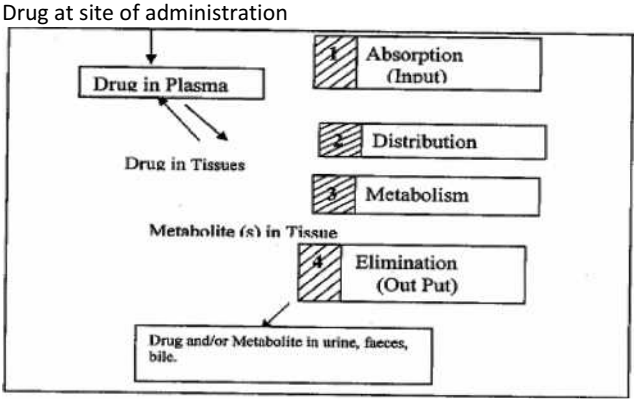


Figure 3.3: Schematic representation of drug absorption distribution, metabolism and elimination.
Source: Lippincott's illustrated Reviews, Pharmacology, third edition by Richard D. Howland and Mr. J. Mycek.

Drug Metabolism

Drugs are usually eliminated by transformation and / or excretion into the urine or bile.

The liver is the major site for drug metabolism but specific drugs may

undergo biotransformation in other tissues. Some agents are usually administered as inactive compounds (pro-drugs) and must be metabolized to their active forms.

A. Kinetics of metabolism

1. First - order kinetics. The metabolic transformation of drugs is catalyzed by enzymes and most of the reactions obey Michaelis-Menten kinetics

v = Rate of drug metabolism $\frac{Vmax \lceil C1}{Km+[C]}$

In most clinical situations the concentration of the drug (C) is much less than the Michaelis constant Km and the Michaelis - Menten equation reduces to

V = Rate of drug metabolism = $\frac{Vmax \lceil C1}{}$. Km

The rate of drug metabolism is directly proportional to the concentration of free drug, and first - order kinetics are observed.

This means that a constant fraction of drug is metabolized per unit of time.

2. Zero - order kinetics some drugs e.g. aspirin and phenytoin, the doses are very large. Therefore the [C] is much greater than Km, and the velocity equation becomes.

v = rate of drug metabolism = $\frac{Vmai \lceil C1}{}$ = Vmax [C]

The enzyme is saturated by a high free - drug concentration, and the rate of metabolism remains constant over time. This is called zero order kinetics. It is also referred to as clinically nonlinear kinetics. In this case a constant amount of drug is metabolized per unit of time.

Drug Elimination

The removal of a drug from the body may occur through a number of routes. The most important of them is from the kidney through urine. The other routes are bile, intestine, lung or breast milk in nursing mothers. A patient who is suffering from renal failure will undergo extracorporeal dialysis which can remove small molecules e.g. drugs.

Renal elimination of drug can be done by:

(1) Glomerular filtration: Drugs enter the kidney through renal arteries, which divide to form a glomerular capillary plexus. Free drug flows through the capillary slits into Bowman's space as part

of the glomerular filtrate. Lipid solubility and pH do not influence the passage of drug into the glomerular filtrate.

(2) **Proximal tubular secretion:** Drug that was not transferred into the glomerular filtrate leaves the glomeruli through different arterioles which divide to form a capillary plexus surrounding the nephric lumen in the proximal tubule.

(3) **Distal tubular re-absorption:** A drug moves toward the distal convoluted tubule. Its concentration increases and exceeds that of the perivascular space. A patient presenting with phenobarbital overdose can be given bicarbonate, which alkalizes the urine and keeps the drug ionized, thereby decreasing its re-absorption.

(4) **Role of drug metabolism:** Most drugs are lipid soluble and diffuse out of the kidney's tubular lumen when the drug concentration in the filtrate becomes greater than that in the perivascular space.

SELF ASSESSMENT EXERCISE

1. Site the major routes of drug administration
   (a) .....
   .....
   (b) .....
   (c) .....
   ....

2. Describe the physicochemical factors that modify drug absorption
   (a) .....
   .....
   (b) .....
   (c) .....

4.0 CONCLUSION

When a drug is administered to man, a series of events usually takes place before the drug arrives at its target organ. The movement of the pharmacologically active form of a drug from the product into the systematic circulation (Absorption) is one of the most important of such event.

5.0 SUMMARY

For a drug to achieve its pharmacological effect it must be presented in a suitable dosage form at an appropriate site of administration. It must then be absorbed from the site. For the effect of the drug to wear off the drug must always be metabolized and / or excreted and the residue must be

removed from the body.

ANSWER TO SELF ASSESSMENT EXERCISE

Major routes of drug administration:

1. **Oral -** Drug given through the mouth
2. **Sublingual -** Drug given below the tongue
3. **Rectal -** Drug given through the anus
4. **Parenteral -** By injection

Intravenous injection - Drug administered through the vein Intramuscular injection - Drug administered through the muscle

a. Subcutaneous injection - Drug administered through the cutaneous layer.
b. Intrathecal injection - Drug administered through the ventricle

iii. **Topical route -** Drug applied to the skin
iv. **Inhalation** -Drug administered through the nose.

2. Physicochemical factors that modify drug absorption

i **Blood flow to the absorption site:** The higher the blood flow to the absorption site, the more the absorption that will take place at the site. This is because there will be more drug where there is more blood volume.

ii **Total surface area available for absorption:** The greater the surface area of a site, the more the absorption of drug that will take place there and vice versa. For example the intestine that has a surface area of 1000 fold greater than the stomach will have greater absorption that the stomach.

iii **Contact time at the absorption site:** When a drug moves through a system like gastro intestinal tract quickly e.g. when there his diarrhoea, it will not be well absorbed, whereas the one that moves slowly i.e. when there is no diarrhoea will be more absorbed.

6.0 TUTOR-MARKED ASSIGNMENT

Discuss the physicochemical factors that modify drug absorption.

7.0 REFERENCES/FURTHER READINGS

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UNIT 4 BASIC AND CLINICAL EVALUATION OF NEW DRUGS

CONTENTS

1.0 INTRODUCTION

New drugs developments have revolutionized the practice of medicine converting many once fatal or debilitating diseases into almost routine therapeutic exercises. For example over the past 30 years, deaths from cardiovascular disease and stroke have decreased by more than 50% in the USA. This decrease in the percentage of death is due to the increase in the use of anti-hypertensives, cholesterol synthesis inhibitors and drugs that prevent or dissolve blood clots. The process of drug discovery and development has been greatly affected by investment in new technology and by governmental support of medical research. In Nigeria and in most countries, the testing of therapeutic agents is now regulated by legislation and closely monitored by governmental agencies e.g. NAFDAC in Nigeria. One of the first steps in the development of a new drug is the discovery or synthesis of a potential new drug molecule and correlating this molecule with an appropriate biologic target. Repeated application of this approach leads to compounds with increased potency and selectivity. By law the safety and clinical efficacy of drugs must be defined before they can be marketed. In drug development, the company starts with in vitro studies, followed by animal testing, which is then followed by clinical testing (using human beings) before final marketing. Millions of at naira are involved in the research and development of a single successful new drug.

2.0 OBJECTIVES

At the end of the unit, the learner would understand:
- what is involved in the development of new drugs
- preclinical safety and toxicity testing

- the preclinical evaluation of drugs in humans.

3.0 MAIN CONTENT

3.1 Drug Discovery

Most new drugs are launched through one or more of five approaches.

1. Identification or elucidation of a new drug target.
2. Rational drug design based on an understanding of biological mechanism, drug receptor structure and drug structure.
3. Chemical modification of a known molecule.
4. Screening for biological activity of large numbers of natural products; banks of previously discovered chemical entities, and large libraries of peptides, nucleic acid and other organic molecules.
5. Biotechnology and cloning using genes to produce larger peptides and proteins. Moreover, automation, miniaturization and informatics have facilitated the process known as “high throughput screening” which permits millions of assays per month.

3.2 Drug Screening

Irrespective of the source or the key idea leading to a drug candidate molecule, testing it involves a sequence of experimentation and characterization called drug screening. A variety of biological assays at the molecular, cellular, organ system, and whole animal levels are used to define the activity and selectivity of the drug. The type and number of initial screening tests depend on the pharmacological goal. Anti-infective drugs will generally be tested first against a variety of infectious organisms, hypoglycemic drugs for their ability to lower blood sugar etc. In addition, the molecule will also be studied for a broad array of other actions to establish the mechanism of action and selectivity of the drug. This has the advantage of demonstrating unsuspected toxic effects and occasionally discovers a previously unsuspected therapeutic action.

3.3 Preclinical Safety and Toxicity Testing

Candidate drugs that survive the initial screening and profiling procedures must be carefully evaluated for potential risks before and during clinical testing. Depending on the proposed use of the drug, preclinical toxicity testing includes most or all of the following; Acute toxicity test, Sub acute toxicity, Chronic toxicity, effect on reproductive performance, Carcinogenic, Mutagenic potential, investigative toxicology.

3.4 Evaluation in Humans

Less than one third of the drugs tested in clinical trials reach the market place. Federal law in the USA and most countries requires that the study of new drugs in humans be conducted in accordance with stringent guidelines. The design and execution of a good clinical trial requires the efforts of clinician-scientists or clinical pharmacologist, statisticians and frequently other professionals as well. The need for careful design and execution is based on three major confounding factors inherent in the study of any therapeutic measure, pharmacologic or non-pharmacologic - in humans. The confounding factors in Clinical Trials are the variable natural history of most diseases, the presence of other diseases and risk factors, and subject and observer bias.

3.5 National Agency for Food, Drug Administration and Control (NAFDAC)

NAFDAC is the administrative body that oversees the drug evaluation process in Nigeria and grants approval for marketing of new drug products. It was formerly the duty of Federal Ministry of Health, Pharmacy Department until the Agency was set up. If a drug has not been shown through adequately controlled testing to be “Safe” and “effective” for a specific use, it cannot be marked for commercial purpose. Unfortunately “Safe” means different things to the patient, physician and the society. Complete absence of risk is impossible to demonstrate but this fact is not well understood by average member of the public, who assumes that any medication sold with the approval of NAFDAC or FDA must indeed be free of serious side effects. This confusion continues to be a major cause of litigation and dissatisfaction with medical care.

Clinical Trials: The new drug approval process involves a systematic series to be studied in human; a notice of claimed Investigational Exemption for a New Drug (IND) must be filed with the FDA. The IND includes:

(1) Information on the composition and source of the drug
(2) Manufacturing Information
(3) All data from animal studies
(4) Clinical plans and protocols
(5) The names and credentials of physicians who will conduct the clinical trials. Plans for testing in humans can be divided into three phases

In Phase 1, the effects of the drug as a function of dosage are established in a small number (25-50) of healthy volunteers. In Phase 2, the drug is

studied for the first time in patients with the target disease to determine its efficiency, (100-200) patients. In phase 3, the drug is evaluated in much larger number of patients- sometimes thousands - to further establish safety and efficacy.

SELF ASSESSMENT EXERCISE

State the approaches involved in the launching of a new drug.

a. .....
b .....
C.
d

e

4.0 CONCLUSION

New drug developments have revolutionized the practice of Medicine. The periodical literature should be the chief source of clinical information about new drugs especially those very recently released for general use. Such information will include doses, new indications, and major new toxicities and contraindication which health practitioners should be familiar t with.

5.0 SUMMARY

Clinical Evaluation of new drugs involves drug screening, preclinical safety and toxicity testing, evaluation in humans which involve clinical trials. Clinical trials are in three phases, Phase 1, Phase 2 and Phase 3.

ANSWER TO SELF ASSESSMENT EXERCISE

The approaches involved in the launching of a new drug

- Identification or elucidation of a new drug target
- Rational drug design based on an understanding of biologic mechanisms, drug receptor structure and drug structure
- Chemical modification of a known molecule
- Screening for biologic activity of large numbers of natural products, banks of previously discovered chemical entities, and large libraries of peptides, nucleic acids and other organic molecules.
- Biotechnology and cloning using genes to produce larger peptides and proteins.

Moreover, automation, miniaturizing and informatics have facilitated the process known as “high through-put screening” which permits millions of assays per month.

6.0 TUTOR-MARKED ASSIGNMENT

Discuss the approaches used to launch various drugs into the market.

7.0 REFERENCES/FURTHER READINGS

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MODULE 2 INTERACTION OF DRUGS WITH THE BODY SYSTEMS

Unit 1 Autonomic Nervous System
Unit 2 Asthma
Unit 3 Drugs Acting on the Endocrine System
Unit 4 Acid Peptic Diseases

UNIT 1 AUTONOMIC NERVOUS SYSTEM

CONTENTS

1.0 INTRODUCTION

Most of the time drug molecules interact with a specific molecule in the biologic system that plays a regulatory role. The molecule is termed a receptor. The autonomic nervous system lends itself to division on anatomic grounds in two major portions, the sympathetic and parasympathetic. For a drug to interact chemically with its receptor, a drug molecule must have the appropriate size, electrical charge, shape and atomic composition.

The primary chemical transmitters in the peripheral nervous system are acetylcholine, and norepinephrine. There is in some species growing evidence of other peripheral transmitters including histamine, dopamine, and adenine nucleotides, but their physiological role is still unclear.

2.0 OBJECTIVES

At the end of the unit the learner should know the following:

- process of synthesis, storage release and removal of acetylcholine
- the pharmacological intervention neurotransmission
- the mechanism of action of sympathomimetic drugs
- the clinical uses of catecholamine and their adverse reactions.

Irrespective of the type of neuron under consideration, the fundamental steps in chemical transmission are the same. Each of these steps is a potential site for pharmacological intervention in the normal transmission process. The steps are as follows.

1. Synthesis of the transmitter
2. Storage of the transmitter
3. Release of the transmitter by a nerve action potential
4. Interaction of the released transmitter from the vicinity of the receptors
5. Recovery of the effector cell membrane

Synthesis of Acetylcholine

Acetylcholine is synthesized in the cytoplasm from Acetyl-CoA and choline through the catalytic action of the enzyme choline acetyl transferase (ChAT). Acetyl CoA is synthesized in mitochondria which are present in large numbers in the nerve ending. Choline is transported from the extracellular fluid into the neuron terminal by a sodium dependent membrane carrier.

A typical example of a neurotransmitter is **Acetylcholine.** Once synthesized, acetylcholine is transported from the cytoplasm into the vesicles by an anti-porter that removes protons. They can be blocked by vesamicol.

Acetylcholine synthesis is a rapid process capable of supporting a very high rate of transmitter release. Storage of acetylcholine is accomplished by the packaging of "quanta" of acetylcholine molecules (usually 100050,000 molecules in each vesicle). Release of transmitter is dependent on extracellular calcium and occurs when an action potential reaches the terminal and triggers sufficient influx of calcium ions. The increased Ca^{2+} concentration "destabilizes" the storage vesicles by interacting with special proteins associated with the vesicular membrane.

After release from the presynaptic terminal, acetylcholine (ACh) molecules may bind to and activate an acetylcholine receptor. ACh will diffuse within range of an acetyl cholinesterase (AChE) molecule. AChE very efficiently splits acetylcholine into choline and acetate which do not possess transmitter effect and thereby terminate the action of the transmitter.

The half-life of acetylcholine in the synapse is short. Acetyl cholinesterase is found in other tissues e.g. red blood cells. Another cholinesterase with a lower specificity for acetyl choline is butyrylcholinesterase (Pseudocholinesterase) which is found in blood plasma; lower GIT and many other tissues.

3.0 MAIN CONTENT

3.1 Anatomy of Autonomic Nervous System

Autonomic nervous system is divided on anatomic grounds into two major portions; the sympathetic (thoracolumbar) division and the parasympathetic (craniosacral) division. Both divisions originate in nuclei within the central nervous system and give rise to preganglionic efferent fibres that exit from the brain stem or spinal cord and terminate in motor ganglia. The sympathetic preganglionic fibres leave the central nervous system through the thoracic and lumbar spinal nerves.

3.2 Neurotransmitter Chemistry of the Autonomic Nervous

The primary transmitters in the peripheral nervous system are acetylcholine and norepinephrine. Other peripheral transmitters are histamine, dopamine, adenine, nucleotides, but their physiological role is unclear. Although these substances are abundant and important in humans their function as neurotransmitters is unknown. It is safe to say that in humans, most of the motor neurons are either cholinergic or adrenergic and are important to physiology, pathology and therapeutics. A few sympathetic fibres release acetylcholine. Adrenal medullary cells which are embryologically analogous to post ganglionic neurons release a mixture of epinephrine and nor-epinephrine. Most autonomic nerves also release several transmitter substances or co-transmitters, in addition to the primary transmitter.

Five key features of neurotransmitter function represent potential targets of pharmacologic therapy: synthesis, storage, release, activation of receptors and termination of action.

Cholinergic Transmission: The terminals of cholinergic neurons contain large number of small membrane-bound vesicles concentrated near the synaptic portion of the cell membrane as well as a smaller numbers of large dense-cored vesicles farther from the synaptic membrane. The large vesicles contain a high concentration of peptide co-transmitter while the smaller co-clear vesicles contain most of the acetylcholine. Vesicles are initially synthesized in the neuron and some are transported to the terminal. They may also be recycled several times within the terminal.

3.3 Functional Organization of Autonomic Activity

An understanding of the interactions of autonomic nerves with each other and with the effectors organs is essential for an appreciation of the actions of autonomic drugs, especially because of the significant reflex (compensatory) effects that may occur with these agents.

CENTRAL INTEGRATION: - Midbrain and medulla are the two divisions of the autonomic nervous system and the endocrine system and are integrated with each other with sensory input, and with information from higher central nervous system centers. Early investigators then called the parasympathetic system a trophotranic (leading to growth) used to rest and digest, and the sympathetic system an egotropic (leading to energy expenditure that is activated for fight or flight)

Integration of Cardiovascular Function

Autonomic reflexes are important in understanding cardiovascular responses to autonomic drugs. The primary controlled variable in cardiovascular function is mean change in any variable contributing to mean arterial pressure (which evokes powerful homeostatic secondary responses that tend to compensate for the directly evoked change). The homeostatic response may be sufficient to reduce the change in mean arterial pressure and to reverse the drug's effects on heart rate. A slow infusion of norepinephrine is an example. This agent produces direct effects on both vascular and cardiac muscles. It is a powerful vasoconstrictor and, by increasing peripheral vascular resistance, increase mean arterial pressure.

Pharmacological Modification of Autonomic Function

Transmission involves different mechanism in different segments of the autonomic nervous System. Some drugs produce highly specific effects while others are much less selective.

Reserpine: It acts on adrenergic terminal vesicles and provokes storage depletion.

Tyramine and amphetamine: They also act on adrenergic nerve terminals and promote transmitter release.

Norepinephrine: It binds to adrenergic receptors and it causes activation.

Propranolol: It binds to adrenergic receptors and prevents activation.

3.4 Pharmacology of the Eye

The eye is a good example of an organ with multiple autonomic nervous system function. It is controlled by several autonomic receptors. The anterior chamber is the site of several tissues controlled by the autonomic nervous system. These tissues include three different muscles (pupillary dilator and constrictor muscles in the iris and the ciliary muscle) and the

secretory epithelium of the ciliary body.

Muscarinic cholinomimetics mediate contraction of the circular papillary constrictor muscle and of the ciliary muscle. Contraction of the pupillary constrictor muscle causes miosis, a reduction in pupil's size. Miosis is usually present in patients exposed to large systemic or small topical doses of cholinomimetics, especially organophosphate cholinesterase inhibitors

SELF ASSESSMENT EXERCISE

1. Explain briefly the processes that take place in the transmission of a neurotransmitter

a. ……
b. ……
c. .....
d. ……
e. .....

2. State what happens in the pharmacological modification that takes place when reserpine and propranolol are administered.

Reserpine .....

Propranolol .....

4.0 CONCLUSION

In humans, the majority of peripheral motor neurons are either cholinergic or adrenergic. They are very important in physiology, pathology and therapeutics.

5.0 SUMMARY

Irrespective of the type of neuron under consideration, the fundamental steps in chemical transmission involve the following:

1. Synthesis of the transmitter
2. Storage of the transmitter
3. Release of the transmitter by a nerve action potential
4. Interaction of the released transmitter with receptors on the effector cell membrane
5. Rapid removal of the transmitter from the vicinity of the receptors
6. Recovery of the effector cell membranes

The major therapeutic uses of the cholinomimetics are for diseases of the eye (glaucoma, accommodative esotiopia), the gastrointestinal and urinary tract (post-operative atony, neurogenic bladder), the neuromuscular junction (myasthenia gravis curare induced neuromuscular paralysis) and namely the heart. Cholinesterase inhibitors are occasionally used in the treatment of atropine over dosage and patients with Alzheimer's disease.

ANSWER TO SELF ASSESSMENT EXERCISE

1. Transmission of a neurotransmitter

a. Synthesis of the transmitter
b. Storage of the transmitter
c. Release of the transmitter by a nerve action potential
d. Interaction of the released transmitter with receptors on the effector cell membrane
e. Rapid removal of the transmitter from the vicinity of the receptors
f. Recovery of the effector cell membrane

2. Pharmacologic modification that takes place when Reserpine and Propranolol are administered.

Reserpine: It acts on adrenergic terminal vesicles. The process is by transmitter storage. The site is at the vesicles (adrenergic terminals) and it prevents storage depletion.

Propranolol: It binds B receptors at adrenergic effectors. It prevents activation.

6.0 TUTOR MARKED ASSIGNMENT

Explain briefly the processes that take place in neurotransmission.

7.0 REFERENCES/FURTHER READINGS

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UNIT 2 ASTHMA

CONTENTS

1.0 INTRODUCTION

Asthma is a syndrome or symptom complex characterized by increased responsiveness of the trachea-bronchial smooth muscle to a variety of stimuli. These physiological symptoms can change in severity either spontaneously or as a result of therapy and are clinically manifested by the sudden onset of a cough, dyspnea and wheezing.

Asthma is a common disease of worldwide distribution. Although its mortality is low, it has a high morbidity as thousands of patients are hospitalized yearly and millions visit clinics. Asthma should be suspected in cases with recurrent acute episodes of bronchiolar obstruction, whether allergic irritation or emotional in origin, which are usually relieved by bronchodilator. Asthma is a common respiratory disease and drugs used in their treatment are phosphodiesterase inhibitors, beta adrenergic agonists, chromones, corticosteroids, hydration and expectoration.

2.0 OBJECTIVES

At the end of the unit the learner will understand:

- the etiology of asthma
- the pathogenesis and clinical manifestation of asthma
- the various drugs used in the treatment of Asthma.

3.0 MAIN CONTENT

3.1 Etiology

The bronchi of asthmatics respond to variety of specific and nonspecific stimuli. Therefore asthma may be classified according to the precipitating factors. Based on precipitating factors, asthma has been broadly classified as extrinsic (allergic, immunology, atopic) and intrinsic (non-allergic, non-atopic).

Extrinsic asthma occurs in some individuals who are exposed to environmental allergies. This type starts early in childhood and may be genetic in origin as the family history may reveal previous atopic disorders such as asthma and hay fever. Asthmatic attacks are frequently seasonal and their incidence may increase during the season of high pollen counts. Other allergies are food such as eggs or flour, feathers and fungal spores.

The immunoglobulin which mediate this type 1 or immediate hypersensitivity reaction is gamma E (IgE).

Intrinsic asthma has no genetics or familiar explanation: In this group of patients non-specific irritants including smoke, cold air, and dust may precipitate an attack. This type of asthma may depend on the level of irritability at which the bronchi react to various irritants. Psychological, pulmonary infections and physical exertion may all precipitate asthma in predisposed individuals.

3.2 Pathogenesis and Clinical Manifestations

The basic defect in asthma is the obstruction of airflow. This is brought about by anatomical changes in the bronchi and bronchioles, with hyperinflation and occlusion by tenacious mucus plugs.

Hyperinflation of the lungs may increase the dead space and overall ventilation requirement. In severe cases this may affect blood flow, arterial hypoxemia may be present and the pH may tend to increase when the lungs are over dusted for a long period, carbon dioxide retention may result in acidosis. Respiratory acidosis is considered to be a dangerous sign in children and should be treated vigorously. The sequence of events in non-allergic asthma has not been properly determined. The autonomic nervous may be responsible for processing the reactions. The activity of the vagus nerve may cause bronchial spasms, as well as initiate the release of chemical mediators. Clinical findings in acute asthma attacks include wheezing, dyspnea and coughing, which appear some minutes after exposure to the precipitating factor or allergen. The patient may complain of tightness of the chest, which is followed by laboured breathing and a distinctly prolonged expiratory phase. A dry hacking cough may be a prominent symptom but when obstruction becomes severe, these paroxysms may be brief or prolonged and associated with orthopnea, hypoventilation and cyanosis. Other symptoms include the production of thick mucous sputum containing fine spiral threads of mucin.

Status asthmaticus occurs when acute paroxysms persist for days and even weeks and cannot be relieved by routine drugs. Patients with status asthmaticus may die of cyanosis following severe impairment of respiration.

Treatment

Treatment usually involves the use of bronchodilators, expectorants and corticosteroids. For hospitalized patients, more vigorous measures are taken including the use of various anti-asthmatic drugs.

3.3 Phosphodiesterase Inhibitors

Theophylline is a phosphodiesterase inhibitor. It is the most frequently used xanthine derivatives in the treatment of asthma. It is effective orally; hence it is widely used and available in various salts. Theophylline is important in the

antigen induced release of mediators, where it inhibits their release from the mast cells. It may also cause relaxation of smooth muscles and inhibition of leukocyte proteolytic enzyme release. Theophylline ethylenediamine (aminophylline) is the most soluble preparations available for intravenous administration. Many other preparations are quite insoluble in water and contain various concentrations of theophylline base. The effectiveness of theophylline is dependent on its plasma concentration. Effective plasma concentrations are 10 to 20μg/ml. Patients should be started with a loading dose of 5 to 6mg/kg in 30 minutes by slow intravenous administration, then 0.9mg/kg per hour to achieve a steady effective plasma level. The half-life of theophylline is about 5.5 hours in adults and 3.4 hours in children, with various individual variations.

The main xanthine preparations are hydrous and anhydrous salts of theophylline, aminophylline, thoephylline methoxamine, diphylline, oxtriphylline and the sodium and calcium salts of theophylline. Several other preparations of theophylline include the microcrystalline, coated tablets, sustained action, tablets, capsules, rectal suppositories, elixirs, choline salts, combination tablets and suspension. The drawback in the use of preparations is that in many cases adequate dosages are not used. It is usual to start with 800 to more than 2000mg of theophylline per day and this may increase depending on response and body size of the patient in order to determine the optimum dose.
The most common side effects of theophylline include anorexia, vomiting, nausea, abdominal pain, nervousness and tachycardia. These side effects are dosage related, and many disappear when the drug is discontinued.

The three important methylxanthines are theophylline, theobromine and caffeine. The major source is beverages (tea, coffee respectively). Theophylline's very low cost is an important advantage for poor patients in areas where health care resources are limited.

3.3.1 Beta Adrenergic Agonists

The beta adrenergic agonists, including the catecholamines, ephedrine, resorcinols and saligenins, exert their pharmacological effects by stimulating both the alpha and beta receptor systems. Beta receptors are divided into Pi receptors in the heart muscle and p_2 receptors in the bronchial smooth muscles and mast cells. Pi agonists stimulate cardiac muscle while p_2 agonists predominantly cause bronchodilation and vasodilation. This system has led to the development of semi synthetic drugs with selective actions. Consequently an ideal bronchodilator would be pure p_2 agonists that would dilate the airways with little cardiac stimulation. Although such drug has not yet been developed.

The sympathomimetics commonly used in asthma are isoproterenol, administered by inhalation, epinephrine administered by inhalation, sublingual, subcutaneous; isoetharine by inhalation; metaproterenol by oral administration; terbutaline by oral administration, subcutaneous and inhalation and ephedrine, salbutamol, salmeterol by oral administration.

3.4 Chromones and Corticosteroids

Disodium cromoglycate (cromolyn sodium) is a synthetic derivative of a naturally occurring substance called khellin, which was observed to relax smooth muscle. It does not have a direct bronchodilating effect but inhibits antigen-induced bronchospasm and stabilizes the mast cell membrane. In addition, cromolyn sodium is claimed to inhibit phosphodiesterase activity, resulting in a higher concentration of plasma cyclic AMP. By stabilizing the mast cells, it inhibits the release of the chemical mediators involved in allergic and non-allergic asthma. Cromolyn sodium is not beneficial in acute attack of asthma but it is useful as a prophylactic agent, especially in children with allergic asthma. Depending on the severity of the asthma, patients show wide variations in their response to cromolyn, some may respond immediately while others may take several days or weeks to achieve an adequate response. Cromolyn is not effective orally, but is administered

by inhalation. It is available as a 20mg drug powder contained in a gelatin capsule. 20mg is inhaled four times a day and the therapy should be continued without interruption. The most common side effect is irritation of the upper respiratory tract, which may result in coughing and occasional bronchospasm. Other side effects include pulmonary eosinophilia and hypersensitivity reactions such as skin eruptions, urticaria and anaphylaxis. Since cromolyn is not a bronchodilator, it should not be used in preference to xanthines in asthma therapy. Although the drug is expensive, the patient should try the therapy for at least one month to assess its success.

Corticosteroids: Corticosteroids are the most potent of all antiasthma drugs. They are often effective in asthmatic patients who are resistant to bronchodilators. The major drawback in the use of steroids is their numerous side effects, which include osteoporosis, weight gain, hypertension, sodium and water retention, edema and adrenal suppression. Their mechanism of action is not clear but it is claimed that steroids relax bronchial smooth muscles and suppress the activity of inflammatory cells. Another aspect of their action is the enhancement of the effect of beta adrenergic drugs on cyclic AMP production. Steroids therapy is of benefit in severe forms of asthma such as status asthmaticus. Prednisolone and methyl prednisolone are the most commonly employed steroids in oral therapy whereas other steroids such as hydrocortisone show no advantages. However, before systemic steroid therapy is initiated, patients should be carefully evaluated. For continuous therapy, the smallest possible doses should be used, i.e. about 30 to 60 mg per day of prednisolone or its equivalent. Steroids are not alternatives to bronchodilators. For maximum effect both drugs should be given simultaneously. With clinical improvement, the dosage should be decreased and in situations where continuous steroid therapy is necessary, alternate therapy should be used to lessen the incidence of side effects, especially adrenal suppression. Inhaled steroids have emerged in an attempt to reduce the incidence of side effects seen with systemic steroids. Beclomethasone dipropionate has given the best results among the topical or inhaled preparations. The usual dosage is 100mg (two inhalations) four times a day. It takes

about seven days to reach maximum effect, but is not effective in acute attacks. It has minimum side effects. Inhaled steroids should not replace systematic steroids because consequent side effect may be severe.

3.5 Hydration and Expectoration

In most cases patients who arrive at hospitals with asthma attacks appear dehydrated, adequate hydration is important and it is the first stage of hospital treatment. Dehydration is responsible for the production of viscous mucus and mucus plugs. As a result of poor fluid intake, water loss and the diuretic effects of certain drugs, some patients become hypovolemic. Hydration may be accomplished with 2 to 4 litres of dextrose in water, with adequate sodium and potassium electrolyte replacement. Proper hydration will enhance mucus and sputum liquidification. Sodium bicarbonate may be added in cases with respiratory and metabolic acidosis. Iodides and acetylcystein are employed as expectorants and mucolytic agents respectively.

3.6 Miscellaneous Drugs

Other drugs used in the treatment of asthma are sedatives, antihistamines, anticholinergics and prostagladins. Sedatives are not routinely used in the treatment of asthma as they may cause various problems. Since psychological factors may form part of asthma attacks, mild sedation with benzodiazepines may be used in cases of overt anxiety accompanied by hyperventilation and alkalosis. Otherwise, narcotics, barbiturates, phenothazines and tricyclic antidepressants should be avoided as they may depress respiration and the cough reflex.

SELF ASSESSMENT EXERCISE

1. What do you understand by Intrinsic and Extrinsic Asthma? Intrinsic asthma is
   .....
   .....

Extrinsic asthma is
.....
.....

2. List by giving examples the various drugs used in the treatment of asthma.
a.....
b .....
c.....
d .....
e.....
f .....

4.0 CONCLUSION

It is important for the health care provider to understand the multi factorial nature of asthma. Many asthmatic patients can be relieved by an adequate dosage of aerosol bronchodilators. Healthcare providers should advise asthmatic patients to seek proper medical care to avoid further complications of asthma.

5.0 SUMMARY

Asthma is a syndrome characterized by increased responsiveness of the trachea-bronchial which are clinically manifested by the sudden onset of cough, dyspnea and wheezing. Drugs used in the treatment of asthma are phosphodiesterase inhibitors e.g. theophylline; beta adrenergic agonists e.g., isoproterenol; sympathomimetics e.g. ephedrine; chromones e.g. disodium cromoglycate; corticosteroids e.g. prednisolone, hydration e.g. dextrose in water, expectoration e.g. iodides and other drugs like sedatives, antihistamines.

ANSWER TO SELF ASSESSMENT EXERCISE

1. Extrinsic Asthma occurs in some individuals who are

exposed to environmental allergies. It occurs early in childhood and may be genetic in origin.

Intrinsic Asthma has no genetic or familiar explanation. In this case non-specific irritants e.g. smoke, cold air and dust may precipitate an attack.

2. Drugs used in the treatment of asthma:

a. Phosphodiesterase inhibitor e.g. Theophylline.
b. Sympathomimetic s and Beta adrenergic agonists e.g Isoproterenol and ephedrine.
c. Chromones e.g. Disodium cromoglycate.
d. Corticosteroids e.g. Prednisolone.
e. Hydration e.g. dextrose in water.
f. Expectoration e.g. Iodides
g. Others e.g. Sedatives

6.0 TUTOR-MARKED ASSIGNMENT

Discuss the pathogenesis of asthma.

7.0 REFERENCES/FURTHER READINGS

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UNIT 3 DRUGS ACTING ON THE ENDOCRINE SYSTEM

CONTENTS

1.0 INTRODUCTION

Diabetes mellitus is a hereditary metabolic disease characterized by hyperglycemia and eventual glycosuria. It is caused by the inability of tissues to carry out normal metabolism of carbohydrates, fats and proteins due to an absolute or relative lack of insulin. It is an important endocrine and metabolic disease causing a lot of morbidity and mortality. Because of the chronic nature of the disease and the complexity in its management, diabetes requires comprehensive patient care and an interdisciplinary approach to treatment. Diabetic patients do carry out self-medication so they must have a good knowledge of their diet, perform urine tests and then measure and administer the correct dose of insulin. Therefore, patient's compliance is important

2.0 OBJECTIVES

At the end of the unit, the learner will be able to:
- Define diabetes and its pathophysiology
- Classify drugs used in the treatment of diabetes.

3.0 MAIN CONTENT

3.1 Etiology

Diabetes mellitus is a hereditary disease, although the precise cause of the dysfunction of the insulin-producing pancreas has not been understood. It is thought that the disease is inherited as a homozygous recessive trait, with multiple environmental factors influencing the clinical expression of the genetic pattern. The factors can be emotional, physical (infection, trauma), chemical such as drugs (diuretics and steroids), stress, disease process (pancreatic tumor) and calorie intake. Body weight may increase the demand for endogenous insulin. This genetic explanation may be inadequate because studies have shown that sometimes only one identical twin born to parents with diabetes develops the disease. Also, only 50% of children with two diabetic parents develop the disease. Other theories proposed for the etiology are:

(1) The production of defective insulin which will not function effectively.
(2) The production of an insulin antagonist which may compete for insulin receptors.
(3) The formation of anti-insulin anti-bodies which immunologically inactivate insulin.

3.2 Pathophysiology

In diabetes, the main defect in body homeostasis is the lack of adequate and effective insulin. Although carbohydrates appear to be central to the metabolic disorders, fats and proteins are also involved. The fasting blood sugar level is often quoted as 100mg/dl although the body maintains a blood sugar rage of 40 to 160mg/dl. The brain requires a minimum blood glucose level of 40mg/dl for its metabolic processes.

The renal glucose level is 170 to 180mg/dl, and above this level glucose passes into the urine and is excreted. A carbohydrate diet is the greatest stimulant for the release of insulin from the P cells of the pancreas. Amino acids, ketones and long chain fatty acids may also stimulate insulin release, while glucagon,

growth hormone, ACTH and cortisone may do so to a lesser degree. Epinephrine and norepinephrine suppress insulin release. Prolonged fasting will also suppress insulin secretion and release. In the presence of insulin, glucose is converted into free fatty acids in the adipose tissue and stored as triglycerides. The essential metabolic functions of insulin are listed below.

1. Acceleration of glucose permeability into striated muscle and adipose tissue.
2. It facilitates glucose translocation from extracellular to intracellular compartments.
3. It stimulates glycogen synthesis and storage in the liver.
4. It enhances the formation of triglycerides.
5. It inhibits the release of free fatty acids from adipose tissue.
6. It promotes the incorporation of amino acids into muscle protein.
7. It increases the availability of endogenous precursors and ATP for protein synthesis.
8. It promotes ribosomal peptide binding and RNA synthesis.

Insulin deficiency causes the following:

1. The synthesis of proteins, lipids and glycogen is inhibited.
2. The decrease in peripheral glucose uptake is exacerbated.
3. Despite hyperglycemia, glycolysis from the liver is accelerated and the blood glucose level rises above the renal threshold glucose then spills into the urine causing water loss by osmosis, resulting in polyuria and polydypsia.
4. The increased mobilization of fats from adipose tissue leads to elevated levels of cholesterol, lipids, free fatty acids and triglycerides.
5. The possibility of ketoacidosis increase, the interruption of lipid synthesis and excessive mobilization of fats from adipose tissue cause ketone

production.

3.3 Management of Diabetes Mellitus

Some tests are used in diagnosing diabetes. These are oral glucose tolerance test (OGTT), Fasting blood glucose (FBS) and urine tests. The disease is incurable so treatment should be directed toward certain objectives i.e. relief of symptoms of hyperglycemia and glycosuria as well as prevention of acute complications of hyperglycemia, ketoacidosis and hyperosmolar coma. In juvenile diabetes, the goal of therapy should include maintenance of optimal physical health, including normal growth.

Insulin dosing: The majority of cases of juvenile-onset diabetes are insulin dependent and some adult-onset diabetes may require insulin in stressful situations such as surgery, infection and pregnancy. Insulin preparations of bovine and porcine insulin are available. Patient variability may determine which preparation is selected in a particular situation. A patient who presents with acidosis or septicemia may have to start with regular and intermediate acting insulins. Experienced physicians may start a patient with 20units of an intermediate acting such as PZI or NPH once a day and then gradually increase the dosage until the degree of glucosuria is consistent and nocturia is minimized. Refrigeration of insulin is important except for the vial that is in use.

3.4 Oral Hypoglycemic Agents

Sulphonylurea:. They are useful for the management of hyperglycemia in maturity onset diabetes. They are orally effective in lowering blood glucose levels and are also safe, convenient and more acceptable than insulin to many patients. Oral hypoglycemic agents are not recommended for juvenile diabetes, pregnant women and those who have renal disease or those whose hyperglycemia can be controlled by diet. Examples of sulphonlyureas and their doses.

Tolbutamide: Dose 0.5 to 2.0g per day; chlorpropamide dose: 0.12 to 0.5g per day; glibenclamide Dose 0.0025 to 0.020g per

day.

Biguanides: Examples of biguanides are metformin (Glucophage) and buformin (silubin) Metformin may be used in combination with sulfonylureas to treat secondary failures or in combination with insulin to decrease its dosage in certain patients. They promote peripheral utilization of glucose by the muscles by inhibiting active transport mechanisms. They also block gastrointestinal absorption of glucose.

SELF ASSESSMENT EXERCISE

1. List the physiological and biochemical actions that can occur as a result of insulin deficiency

a.
.....

b
.....

c
.....

d
.....

e
.....

2. Name the drugs used in the treatment of diabetes and state the doses of the oral drugs

(a) Injection:.....
(b) Oral drug:
- ..... dose
- ..... dose
- ..... dose

4.0 CONCLUSION

Insulin and oral hypoglycemic agents are commonly used in prolonging the life of diabetic patients and reducing the long term complications of the disease. It is important for senior

health care providers to understand the nature of the disease and the drugs used so as to give effective advice to the patients.

5.0 SUMMARY

Diabetes is a hereditary disease of endocrine and of metabolic origin. It causes a high degree of morbidity and mortality. Drugs commonly used to prevent its complications and prolong the life of the patients are insulin and oral hypoglycemic agents.

ANSWER TO SELF ASSESSMENT EXERCISE

1. Physiological and biochemical actions that can occur as a result of insulin deficiency:

a) The synthesis of proteins, lipids and glycogen in inhibited.
b) The decrease in peripheral glucose uptake is exacerbated.
c) Despite hyperglycemia, glycolysis from the liver is accelerated and the blood glucose level rises above the renal threshold
d) The increased mobilization of fats from adipose tissue leads to elevated levels of cholesterol, lipids, free fatty acids and triglycerides.
e) The possibility of ketoacidosis increases.

2. (a) Injection: Insulin Injection.
(b) Oral drug: • Tolbutamide dose: 0.5 - 2.0g/ day
• Chlorpropamide dose 0.1-0.5g/ day
•. Glibenclamide: dose 0.0025 - 0.02g/day

6.0 TUTOR-MARKED ASSIGNMENT

Discuss the metabolic functions of insulin.

7.0 REFERENCES/FURTHER READINGS

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UNIT 4 ACID PEPTIC DISEASES

CONTENTS

1.0 INTRODUCTION

Acid-peptic diseases include gastro esophageal reflux, peptic ulcer (gastric and duodenal) and stress-related mucosal injury. In all, mucosal erosions or ulcerations arise when the caustic effects of aggressive factors (acid, pepsin, bile) overwhelm the defensive factors of the gastro intestinal mucosa (mucus and bicarbonate secretion, prostaglandins, blood flow, and the processes of restitution and regeneration after cellular injury). Over 99% of peptic ulcers are caused by infection with the bacterium *Helicobacter pylori* or by use of non-steroidal anti-inflammatory drugs (NSAIDS). Drugs used in the treatment of acid peptic disorders can be divided into two classes; Agents that reduce intragastric acidity, and agents that promote mucosal defense.

2.0 OBJECTIVES

At the end of the unit, the learner will know;

- what acid peptic diseases are
- the class of drugs used in treating acid peptic diseases
- the contraindications in Acid Peptic diseases.

3.0 MAIN CONTENT

3.1 Antacids

Antacids have been used for centuries in the treatment of patients with dyspepsia and acid-peptic disorders. They were the mainstay of treatment for acid-peptic disorders until the advent of H_2-receptor antagonists and proton pump inhibitors. They continue to be used commonly by patients as non-prescription remedies for the intermittent treatment of heartburn and dyspepsia.

Sodium bicarbonate (e.g. baking soda, Alkaseltzer) reacts rapidly with HC1 to produce cabondioxide and NaCl. Formation of carbondioxide results in gastric distention and belching. Unreacted alkali is readily absorbed, potentially causing metabolic alkalosis when given in high doses to patients with renal insufficiency.

Calcium Carbonate (e.g. Turns, Os-Cal) is less soluble and reacts more slowly than sodium bicarbonate with HC1 to form carbondioxide and $CaCl_2$. Like sodium bicarbonate, calcium carbonate may cause belching or metabolic alkalosis .Calcium carbonate is used for a number of indication apart from its antacid properties .Calcium carbonate is used to treat hypocalcemia .Excessive doses of either sodium bicarbonate nor calcium carbonate with calcium contains dairy products can lead to hypercalcemia, renal insufficiency, and metabolic alkalosis (milk-alkali syndrome).

Formulations containing magnesium hydroxide or aluminum hydroxide react slowly with HC1 to form magnesium HC1 chloride or aluminum chloride and water. Because no gas is generated belching does not occur. Metabolic alkalosis is also uncommon because of the sufficiency of the neutralization reaction.

All antacids may affect the absorption of other medications by binding the drugs or by increasing intragastric pH that affects

the drugs dissolution or solubility. Hence, antacids should not be given within 2 hours of doses of tetracyclines, fluoroquinolones, Itraconazole and iron.

3.2 H_2- Receptor Antagonists

Until the early 1990s, H_2-receptors antagonists (commonly referred to as H_2-blockers) were the most commonly prescribed drugs in the word. With the recognition of the role of *H. pylori* in ulcer disease (which may be treated with appropriate antibacterial therapy) and the advent of proton pump inhibitors, the use of prescription H_2-blockers has declined markedly. Four H_2 antagonists are in clinical use: cimetidine, ranitidine, famotidine and nizatidine. All four agents are rapidly absorbed from the intestine, cimetidine, ranitidine and famotidine undergo first pass hepatic metabolism resulting in a bioavailability of approximately 50%. Nizatidine has little first pass metabolism and a bioavailability of almost 100%. H_2-receptor antagonists continue to be prescribed commonly. However, due to their superior acid inhibition and safety profile, proton pump inhibitors are steadily replacing H_2 antagonists for most clinical indications Dosses: cimetidine 800mg daily or 400mg bid, Ranitidine 300mg daily or 150mg bid, Nizatidine 300mg daily or 150mg bid, Famotidine 40mg daily or 20mg bid.

3.3 Proton Pump Inhibitors (PPI)

Five proton pump inhibitors are available for clinical use. They are omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole. Since their introduction in the late 1980s, these efficacious acid inhibitory agents have rapidly assumed the major role for the treatment of acid-peptic disorders. They are now among the most widely selling drugs worldwide due to their outstanding efficacy and safety. All are substituted benzimidazoles that resemble H_2 antagonists in structure but have a completely different mechanism of action. Omeperazole is a racemic mixture of R-and S-Isomers. Esomeprazole is the S Isomer of omeprazole. All agents are available in an intravenous formulation. The bioavailability of proton pump inhibitors is decreased approximately 50% by

food; hence the drug should be administered on an empty stomach. Doses: Esomeprazole - 20 - 40mg qd, Lansoprazole - 30mg qd, Omeprazole 20mg qd, Pantoprazole 40mg qd, Rabeprazole 20mg qd. From pharmacokinetic perspective, proton pump inhibitors are ideal drugs, they have a short serum half-life, they are concentrated and activated near their site of action, and they have a long duration of action. In contrast to H_2 antagonists, proton pump inhibitors inhibit both fasting and meal - stimulated secretion because they block the final common pathway of acid secretion.

3.4 Mucosal Protective Agents

Sucralfate is a salt of sucrose complexes to sulfated aluminum hydroxide. In water or acidic solutions it forms a viscous, tenacious paste that binds selectively to ulcers or erosions for up to 6 hours. Sucralfate has limited solubility, breaking and an aluminum salt. Less than 3% of intact drug and 0.01% of aluminum is absorbed from the intestinal tract, the remainder is excreted in the feces. Sucralfate is administered in a dosage of lg four times daily on an empty stomach.

At present its clinical uses are limited because of availability of drugs like the proton pump inhibitors. Its adverse effect is constipation in 2% of patients due to the aluminum salt. Because a small amount of aluminum is absorbed, it should not be used for prolonged periods in patients with renal insufficiency.

SELF ASSESSMENT EXERCISE

Proton Pump Inhibitors are now currently used in the treatment of peptic ulcer disease, discuss.

4.0 CONCLUSION

Acid-peptic diseases include gastroesophageal reflux, peptic ulcer (gastric and duodenal), and stress - related mucosal injury. In all these conditions, mucosal erosions or ulcerations arise when the caustic effects of the gastrointestinal mucosa.

5.0 SUMMARY

Drugs used in the treatment of peptic acid disease are Antacids, H_2- Receptor antagonists, Proton Pump Inhibitors and Mucosal protective agents. With the advent of Proton Pump Inhibitors, less of Antacids, H_2- Receptor antagonists and mucosal protective agents are being used.

ANSWER TO SELF ASSESSMENT EXERCISE

Proton Pump Inhibitors:

Five proton pump inhibitors are available for use. They are Omeperazole, Lansoprazole, pantoprazole and Esomeprazole. Doses: Esomeprazole 20-40mg qd, Lansoprazole 30mg qid, Omeprazole 20mg qd. Since their introduction in the late 1980s, these efficacious acid inhibitory agents have rapidly assumed the major role for the treatment of acid peptic disorders. They are now among the most widely selling drugs worldwide due to their outstanding efficacy and safety. The bioavailability is decreased approximately 50% by food, hence the drug should be administered on an empty stomach. They have a short serum half-life, they are concentrated and activated near their site of action and they have a long duration of action.

6.0 TUTOR-MARKED ASSIGNMENT

Discuss and give examples of H_2 receptor antagonists in the treatment of ulcer.

7.0 REFERENCES/FURTHER READINGS

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MODULE 3 DRUG ACTING ON THE CARDIOVASCULAR SYSTEM

Unit 1 Congestive Heart Failure
Unit 2 Cardiac Arrhythmia and
Unit 3 Drug Use Angina Pectoris
Unit 4 Antihypertensive Drugs

UNIT 1 CONGESTIVE HEART FAILURE

CONTENTS

1.0 INTRODUCTION

Congestive heart failure is said to occur when the heart can no longer deliver enough oxygenated blood for tissue metabolism during exercise and rest. The syndrome implies myocardial or ventricular failure since this region is responsible for the forceful delivery of blood to the tissues. It is estimated that in a given population of people above 50years, 2 to 5 people in every 1000 will be suffering from congestive heart failure. At the age of 60 years, males are more vulnerable than the females.

2.0 OBJECTIVES

At the end of the unit the learner will know:

- The definition of congestive heart failure and its patho-physiology
- The drugs used in the treatment of congestive heart failure main content.

3.0 MAIN CONTENT

Etiology

Congestive heart failure (CHF) is usually caused by damaged cardiac tissue which usually decreases its nutritive supply thereby decreasing its efficiency. The most important single

etiological factor of CHF is hypertension. Hypertensive patients have greater risk of developing CHF than any other person. Other conditions that may precipitate CHF are coronary heart disease, rheumatic heart disease, myocardial infarction, persistent cardiac arrhythmia, pulmonary embolism, emphysema, valvular deformities, hyperthyroidism and congenital cardiac effect.

3.1 Pathology

The pumping actions of the left and right sides of the heart complement each other to produce a continuous flow of blood to the body tissues. There are two main types of heart failures, the left heart failure and the right heart failure. The left heart failure is more common than the right heart failure because systemic arterial hypertension, rheumatic heart disease usually affects the left side of the heart and the left heart failure is the major cause of the right heart failure. When the amount of blood entering the heart chambers increase, the cardiac muscle are stretched (initial increase) resulting in a more vigorous contraction. However when the muscle fibres are stretched beyond a critical limit, the systolic tension decreases sharply. During the early phase of heart failure, there is a reflex activation of the sympathetic autonomic nervous system.

Several catecholamines including norepivephrine are released. The increased contractility (inotropic effect) and heart rate (chronotropic effects) cannot sustain for a long time the failing heart. The vasoconstrictive effects of the catecholamines in the skin, gastrointestinal tract, and renal circulation will eventually decrease perfusion to these organs. Most patients with congestive heart failure (CHF) complain of chronic fatigue, weakness, dyspnea on exertion or at rest, orthopnea, paroxysmal, indigestion and swelling of the ankle and feet on physical examination. The physician may observe tachycardia, enlarged heart, cyanosis, jaundice, hepatomegaly, heart murmur and ceasation of pulse.

3.2 Therapy in CHF

The goal of therapy is to decrease cardiac work and increase its output. The overall management includes correction of the known underlying disease state (e.g. hypertension), bed rest, sodium restriction, diet, diuretics. The main drugs used in the treatment of CHF are digitalis glycosides and vasodilators.

Digitalis glycosides: These are the most important drugs used in the treatment of CHF. Over 90% of patients suffering from this disease are being treated with it. This is because digitalis increases the mechanical efficiency of the heart. In CHF patient, having a rapid beating hypodynamic, dilated, inefficient myocardium the cardiac output is sharply reduced and many of the complications associated with this condition are attributable to the inadequate tissue perfusion. Restoration of cardiac output towards normal is a primary objective of the treatment of CHF. Digitalization may more than double the cardiac output.

Digitalization means the process of administering an amount of digitalis preparation sufficient to elicit is achieved within 24 hours it is called rapid digitalization and the total dose is the locating dose. If it is achieved within several days it is called slow digitalization and the maintenance dose is usually employed Average digitalization dose.

Digoxin 1.0 to 1.5 mg orally, 0.7 to 1.5 mg IV Digitalis toxicity: The therapeutic index of digitalis is relatively narrow making toxicity occur in about 30% of patients on digitalis and this is appreciably very high. Digitalis preparations available are dioxin, digitoxin, ouabain, dedanoside Digoxin is the most commonly used by clinicians.

Adverse effects of digitalis

Toxicity occurs in about 30% of patients on digitalis and this is very high. For digitalized patients, it is important to know their renal status as impaired renal function will increase the toxicity of the drug. Acid-base status and electrolytes like potassium, calcium, and magnesium should be within normal

limits. Cardiac toxicities of digitalis include arrhythmias and conduction defects, A.V block, increased automaticity premature ventricular bets and paroxysmal arterial tachycardia with or without block. Extra cardiac toxicities i.e. toxicities outside the cardiac tissues are anorexia, nausea, vomiting headache, drowsiness and disorientation.

3.3 Diuretics

These are the second most important drugs in the treatment of CHF because more the 60% of such patients will receive them. It is important to use diuretics because the kidney normally responds to failing heart. Diseases like orthopnea, hepatomegaly, and cardiomegaly show that the kidney is not functioning well. The haemodynamic effects of digitalis do not make them useful in correcting the clinical manifestation of CHF, so diuretics are better used. Combination of two diuretics can be used for better therapeutic outcome. Triamterene or spironolactone may be used with furosemide or thiazide diuretics with no loss of potassium. Side effects of diuretic therapy are hyperglycemia, gastrointestinal disturbance e.g. nausea vomiting and diarrhoea.

3.4 Vasodilators

Vasodilators are now commonly used in the treatment of CHF. Vasodilators provide automatic relief from CHF by decreasing arterial resistance (after load) to left ventricular outflow. They may also decrease left ventricular congestion preload by their venous dilating properties. Vasodilators are used in advanced CHF and also in moderate CHF when the clinician wishes. Vasodilators that are commonly used are hydralazine, nitroprusside, prazosin and nitrates. Other drugs used in the treatment of CHF are nifedipine, and enalapril.

SELF ASSESSMENT EXERCISE

1. What do you understand by congestive heart failure?
2. Congestive heart failure
3. List the drugs that are used in treating congestive

heart failure

a

.....

b

.....

c.

.....

d

.....

4.0 CONCLUSION

Hypertension is the single implicated cause of congestive heart failure. Other causes that may occur are coronary heart disease, rheumatic heart disease, pulmonary embolism, thyrotoxicosis, anaemia and cardiac arrhythmia.

5.0 SUMMARY

The goal of therapy in CHF is to decrease cardiac work and increase its output. Drugs used mainly in the treatment of CHF are digitalis, diuretics, vasodilators, others are calcium channel blockers and angiotensin converting enzyme inhibitors.

ANSWER TO SELF ASSESSMENT EXERCISE

1. Congestive heart failure is said to occur when the heart can no longer perform the pumping functions i.e. when it can longer deliver enough oxygenated blood for tissue metabolism during exercise and at rest.

2. Drugs used in treating congestive heart failure.

- Digitalis, digoxin, digitoxin, ouabain dedanoside
- Diuretics e.g. frusemide, triamterene spironolactone
- Vasodilators e.g. hydralazine, prazosin nitroprusside, nitrates

Other: Calcium channel blockers e.g. nifedipine, angiotensin converting enzyme inhibitors e.g. captopril and enalapril

6.0 TUTOR-MARKED ASSIGNMENT

Discuss digitals in the treatment of congestive heart failure.

7.0 REFERENCES/FURTHER READINGS

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UNIT 2 CARDIAC ARRHYTHMIA AND DRUG USE

CONTENTS

1.0 INTRODUCTION

Cardiac arrhythmia is a cardiac rhythm in which an abnormality exists in the site, frequency or pattern of conduction of the impulse or both. The term "arrhythmia" (dysrrthymia) is applied to a group of cardiac disorders, ranging from mild, asymptomatic sinus arrhythmia to serious, life threatening ventricular tachycardia and ventricular fibrillation. Arrhythmia denotes any deviation from the normal cardiac rhythm. The pacemaker activity must reside in the sinoatrial node (SA node), and must generate impulses with a frequency of 60 to 100 beats per minute. The impulses in the SA node must be generated at regular intervals and must pass through the normal atrioventricular (AV) conduction system, with a normal constant conduction time. When it does not follow the stated pattern, cardiac arrhythmia is said to occur.

2.0 OBJECTIVES

At the end of the unit, the learner will be able to:

- Define cardiac arrhythmia
- Outline the classes of drugs used in the treatment of cardiac arrhythmia.

3.0 MAIN CONTENT

3.1 Etiology

Cardiac arrhythmias can occur because of abnormal impulse generation,

abnormal impulse conduction or a combination of both. Some of the common causes of cardiac arrhythmia are anatomical i.e. congenital cardiac defects, valvular diseases (usually rheumatic in origin), cardiac enlargement and hypertrophy; endocrine disorders i.e. thyrotoxicosis, phaeochromocytoma; vascular disorders i.e. myocardial infarction, iatrogenic i.e. drug induced-digitalis toxicity, personal habits i.e. excessive tea or coffee drinking, smoking. There are more causes but irrespective of the causes, the drug therapy is the same. In non-pharmacological intervention, arrhythmia caused by phaeochromocytoma will involve surgical excision of the phaeochromocytoma while that caused by digitalis will involve the discontinuation of digitalis use by the patient. Physical maneuvers, e.g. DC counter shock (cardioverson), artificial pacemaker and supportive measures are also non-pharmacological intervention.

3.2 Pathogenesis

The sign and symptoms of cardiac arrhythmia depend on the underlying cause. In most cases the patient is unaware of the abnormality but clinical examination or electrocardiogram (ECG) reveals the arrhythmia. The symptoms for which the patient see the physician include, inadequate circulation, like fatigue, dyspnoea, shock, syncope, angina, and myocardial infarction, and those due to abnormal rhythm include missed heart beat and palpitations. The symptom can also be seen in numerous disorders in which cardiac function are perfectly normal. It is therefore important to physically examine the patient and do electrocardiogram investigation (ECG). Physical examination might show enlarged heart, cardiac murmurs, irregular heart sounds. Physical examination may also be useful in finding the underlying cause.

3.3 Therapy

Class I Drugs. Class I drugs are drugs with a membrane stabilizing effect such as quinidine, procainamide, disopyramide, lignocaine, mexiletine, phenytoin and tocainide. For easy understanding this class 1 drugs are divided into two groups.

3.3.1 Class I Drug

(First group i.e. Class IA) include quinidine, procainamide, disopyramide. Class 1 (second group i.e. Class IB) are lignocaine, phenytoin and mexiletine. The Class IA drugs have similar actions on the heart and the mechanism of control of arrhythmia is similar. They all decrease the slope of phase 4 depolarization thereby reducing the firing frequency of ectopic foci allowing the SA node to function as pacemaker. In usual therapeutic

doses they do not suppress the automatic action of the SA node. They slow down conduction and reduce the frequency at which the cells are responsive to excitation. The antimuscarinic action of these drugs produces arrhythmia in patients with atrial fibrillation. Quinidine also produces hypotension so care should be taken when it is administered. Quinidine dose is 200 to 600mg every 6 to 8 hours orally. Procainamide dose is 500 to 1000mg every 3 to 4 hours orally.

Lignocaine, phenytoin and mexiletin

These anti-arrhythmic drugs suppress the phase 4 depolarization in ectopic automatic tissues, but have no significant effect on the phase 4 depolarization of sinus nodal cell in therapeutic concentrations. Unlike guanidine and the first group of drugs they have no significant effect on the membrane responsiveness of the automatic tissue in the heart or they shift the membrane responsiveness curve to the left. The effect is seen particularly when the membrane responsiveness is already depressed. These groups of drugs relieve a sinus block produced by digitalis over dosage

Phenytoin: The usual dose is 100mg every 6 hours orally

Lignocaine: 10 to 50 mg /kg per minute intravenously.

3.4 Class II Drugs are Beta Adrenoceptor Blockers

Propranolol, metoprolol, nadolol: The three drugs have similar actions. Out of the group, propranolol is the most widely used. Nadolol (and metoprolol) is considered to be cardio-selective in the normal therapeutic concentrations, so does not produce bronchospasm as frequently as propranolol. Their antiarrhythmic actions are due to their ability to block beta-adrenoceptors and to prevent catecholamines from producing their effects. Most of their actions can be produced when catecholamines are present. Re-entrant arrhythmia which is dependent on the presence of catecholamines is abolished by the beta blocking activity of propranolol at the usual plasma levels. Dose of propranolol is 40 to 1000mg every 4 to 6 hour orally, or 1 to 10mg intravenously.

3.5 Class III Drugs e.g. Amiodarone

It is not widely used because of its toxicity. It prolongs the APD and ERP of automatic fibres, an action which is probably most pronounced on the atrial fibres. Amiodarone is orally effective and has a long elimination half-life. If is excreted over a period of weeks after a single dose. The major adverse effect is corneal opacity leading to visual disturbances. This

adverse effect may not be permanent and may stop upon ceasation of therapy. Skin rashes and nausea may also occur. Under this group we have adrenergic neuron blocker i.e. Bretylium.

3.6 Class IV Drug

Calcium antagonists (verapamil, nifedipine) and are also called calcium channel blocker. They are mostly used in the therapy of various cardiovascular disorders including arrhythmia. The calcium antagonists prevent the entry of calcium into all cells. The effects are most marked in SA node and the proximal portion of the A.V Node and the result is that the cells in these regions do not depolarize properly and the conduction of impulses is much slower in the AV node and this action is useful in the treatment of various types of supraventricular and AV nodal tachycardia. Side effects are reduction and prevention of impulse generation in the SA node which may lead to SA nodal block and asystole. It can also cause negative chronotropic effect and reduced peripheral vascular resistance which can precipitate a severe fall in blood pressure. Dose of verapamil administered orally is 40 to 80mg three times a day or 5 to 10mg intravenously.

SELF ASSESSMENT EXERCISE

1. Name the classes of drugs used in the treatment of cardiac arrhythmia and their doses.

a.....

b .....

c.....

d .....

2. What do you understand by cardiac arrhythmia?

Cardiac arrhythmia is _____

4.0 CONCLUSION

Cardiac arrhythmia is a cardiac rhythm in which abnormality exists in the site, frequency or regularity/pattern of impulse formation or in the sequence, velocity or regularity of impulse formation or both.

5.0 SUMMARY

The etiology of cardiac arrhythmia ranges from congenital to personal habits like smoking or excessive coffee or tea drinking. Drugs used in the treatment of cardiac arrhythmia are quinidine, procainamide, disopyramide, lignocaine, phenytoin, mexiletine; propranolol, metoprolol, nadolol; Amiodarone; verapamil and nifedipine.

ANSWER TO SELF ASSESSMENT EXERCISE

1. a. Class 1 drug group 1 quinidine, procainamide.
   Quinidine: - 200 to 600mg every 6-8hrs class I group II - Lignocaine, phenytoin and mexiletin
   b. Group II: Beta adrenoceptor blockers propranolol, metoprolol, nadolol, propranolol - 40 to 1000mg 4 to 6 hourly or1 to 10mg IV.
   c. Class III: Amiodarone
   d. Class IV: calcium antagonists are verapamil, nifedipine verapamil oral 40-80mg three times a day 5-10mg I.V

2. Cardiac arrhythmia is said to occur when there is deviation from the normal cardiac rhythm and there is abnormality in the site, frequency, regularity of impulse formation a in the sequence, velocity, or regularity of conduction of impulse, or both.

6.0 TUTOR-MARKED ASSIGNMENT

Discuss propranolol in the treatment of cardiac arrhythmia.

7.0 REFERENCES/FURTHER READINGS

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UNIT 3 ANGINA PECTORIS

CONTENTS

1.0 INTRODUCTION

Angina pectoris is a condition manifested by pain in the chest and a group of symptoms consisting of sudden aches usually located behind the sternum.

The pain usually radiate from left shoulder to the left arm. The pain may be mild, severe or excruciating. The pain has a distinct quality which compels the patient to stop whatever he is doing and hold his breath. The duration of attack is usually three minutes. Attacks that last 30 to 60 minutes is likely to be heart attack or coronary occlusion.

2.0 OBJECTIVES

At the end of the unit the learner will be able to:
- Define angina pectoris
- Outline the three main groups of drugs used in the treatment of angina pectoris.

3.0 MAIN CONTENT

3.1 Etiology

The basic cause of angina pectoris is ischemia (disease) of the cardiac tissue. Other conditions that cause angina in addition to atherosclerosis

are embolism, closure of coronary artery, polyarthritis nodosa, giant cell arteritis, and coronary artery spasm. Hypertension and valvular heart disease are also implicated in angina pectoris. Risk factors for angina pectoris are high serum cholesterol, hypertension, cigarette smoking, obesity, physical inactivity, old age and male sex. Precipitating factors are bodily exertion, digestion, and other individual peculiarities.

3.2 Pathology

The quality of pain, location, duration and precipitating factor are essential for diagnosis; relief of pain following administration of nitro- glycerin is a useful diagnostic test. History of previous myocardial infarction or cigarette smoking can help in diagnosis. In most cases physical examination does not reveal all that may be present. Associated diseases like hypertension, anaemia, and aortic stenosis might be found.

3.3 Therapy

Non-pharmacological

Reassurance: Many angina patients believe that they are not going to live long. They must be reassured that if they follow the physician's advice on lifestyle, physical exercise, their life will be prolonged.
Amelioration of risk factors: if the patient is a smoker, he must be advised to stop smoking.
Physical activity:- Patient must be educated that rigorous exercise can precipitate angina attack, therefore patients must be advised to do their exercises slowly. An exercise programme, based on the results of stress test must be evolved to increase the cardiac reserve.

3.4 Antianginal Drugs

They are classified into two drugs used to relieve acute attacks of angina pectoris and drugs used to prevent or reduce acute attacks.

Nitroglycerine: This is the oldest and most frequently used organic nitrate. Its efficacy in the relief of acute angina attack is well established that it is considered to be diagnostic. It is very fast acting when given sublingually. The three groups of drugs used to treat angina are nitrates, beta receptor antagonists and calcium antagonists.

3.5 Organic Nitrates

Organic nitrates are potent vasodilators. Their mechanism of action has not been well understood. Nitrates produce vasodilation by stimulation of cyclic GMP and alteration of the prostaglandin system. Organic nitrates

cause myocardial contractility which affect ventricular wall tension and which relieve angina patients. The most common is Nitroglycerine at a dose used of 0.4 mg or 0.6mg which is sufficient to relieve the angina and less likely to induce headache or other unpleasant side effects. Patients should be advised not to take more than three nitroglycerine (NTG) tablets over a period of 15 minutes for a prolong angina attack. Additional NTG must not be taken for the patient may be having a myocardial infarction. Patients should be advised to be in sitting position rather than lying down when taking NTG tablets because gravity adds to the venous pooling that must occur to reduce cardiac work load. Nitroglycerine lingual spray can also be used (Nitrolingual).

It is available in a 0.4mg dose - metered canister. It is an alternative to NTG sublingual. The use of organic nitrate is to decrease the number, severity and duration of angina attacks. The mechanism of action of organic nitrate is the same as that of nitroglycerine.

3.6 Beta Adrenoceptor Blockers

Beta blockers were introduced in the treatment of angina pectoris in the early 1970s. It was believed that by decreasing the work of the heart and consequent reduction of myocardial oxygen demand angina could be relieved. The observation has been sustained by increased use of beta blockers-propranolol, nadolol, atenolol and pindolol. Beta blockers however, should be used with care in diabetic patient because it may mask the symptoms of hyperglycemia. Beta blockers have negative chronotropic and inotropic effects and this makes them useful in cardiovascular diseases.

3.7 Calcium Channel Blockers

Calcium channel blockers that are used in the treatment of angina pectoris are verapamil, nifedipine and diltiazem. Calcium channel blockers reduce myocardial work both directly and indirectly by causing vasodilation. They can be vasodilators by reducing afterload, they can reduce the contraction of the ventricles by decreasing ventricle work and they can produce coronary artery vasodilation. Side effects of calcium channel blockers are headache, oedema, hypotension, constipation, bradycardia.

SELF ASSESSMENT EXERCISE

1. Define angina pectoris. Which drug is used as a diagnostic test to detect angina pectoris?
   Angina pectoris is.....

Drug used as diagnostic test for angina pectoris is.....
.....

2. List the 3 group of drugs used in the treatment of angina pectoris

a. .....
b. .....
c. .....

4.0 CONCLUSION

The main cause of angina pectoris is ischemia of the myocardium. When the demand for oxygen by the myocardium exceeds the supply, ischemia occurs leading to pain, metabolic abnormalities, left ventricular dysfunction and electro-cardiographic abnormalities.

5.0 SUMMARY

Angina pectoria (meaning pain in the chest) is characterized by a group of symptoms consisting of sudden distinctive pain which is usually located behind the sternum. Drugs commonly used in the treatment are the organic nitrates (Nitroglycerne), beta adrenoceptor blockers and calcium channel blockers.

ANSWER TO SELF ASSESSMENT EXERCISE

Angina pectoris is said to occur when there is pain in the chest which is usually located behind the sternum. Drug used as diagnostic test for angina pectoris is Nitroglycerine

Group of drug used in the treatment of angina:

1. Organic nitrates including Nitroglycerine and long acting nitrates
2. Beta adrenoceptor blockers e.g. propranolol, Nadolol and Metoprolol
3. Calcium channel blockers e.g. Nifedipine, verapamil

6. 0 TUTOR-MARKED ASSIGNMENT

Discuss the drug that is used as diagnostic treatment of angina pectoris.

7.0 REFERENCES/FURTHER READINGS

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UNIT 4 ANTIHYPERTENSIVE DRUGS

CONTENTS

1.0 INTRODUCTION

Hypertension can be defined as a disturbance in haemodynamic function in which there is persistent abnormal elevation of systemic blood pressure, whether it is diastolic or systolic, above the arbitrary level of normal pressure of 150/90 mmHg.

The pressure within the arterial side of the cardiovascular system which is essential for blood circulation is termed “blood pressure”. It is usually expressed in mm of mercury (Hg) and the most common method of expression is systolic pressure over the diastolic pressure. Systolic pressure is the pressure of blood in the arteries when blood is expelled from the heart during contraction. Diastolic pressure is the pressure in the arteries during the phase of cardiac relaxation. Statistics from life insurance data clearly indicate that the higher the systolic and diastolic pressure the greater the mortality rate from cardiovascular complications. It now appears that hypertension underlies a wide variety of diseases including angina, and acute myocardial infarction, aortic aneurysm, atherosclerotic obstruction of aorta, strokes and renal failure.

2.0 OBJECTIVES

At the end of the unit, the student should know the following:

- physiologic control of blood pressure
- diagnosis of hypertension
- basic pharmacology of some antihypertensive agents
- the meaning of hypertensive urgencies and hypertensive emergencies.

3.0 MAIN CONTENT

3.1 Etiology & Diagnosis of Hypertension

Majority of patients with hypertension have no symptoms related to their blood pressure elevation. When symptoms occur they fall into the following categories:

a. Those related to increased pressure itself such as headaches (severe form) localized to the occipital region, dizziness, palpitations and easy fatiguability.
b. Those due to underlying disease in cases of secondary hypertension e.g polyuria, nocturia, and muscle weakness in primary aldosteronism, weight gain and postural dizziness.
3. Those due to hypertensive vascular disease e.g epistaxes, hematuria, angina pectoris, dyspnoea on exertion and claudication.

The clinical manifestations and the pathological involvement of various organs are as follows:

1. **Cerebral:** Occipital headache with stiff neck, minor strokes, dizziness
2. **Vascular:** Left ventricular hypertrophy, intermittent claudication
3. **Cardiovascular:** congestive heart failure, myocardial infarction, and angina pectoris
4. **Ocular retinopathy:** Retinal arteriolar narrowing, hyperlipidemia
5. **Renal:** - nocturia, oliguria, polyuria, proteinuria, haematuria
6. **Chest:** Cardiomegaly, hypertrophy of pulmonary vessels.

Hypertension is usually classified broadly into essential (primary) and secondary hypertension. A small number of patients develop hypertension as a manifestation of treatable underlying causes (secondary hypertension). Majority of cases with hypertension have no discernable underlying causative factor and these patients are said to have essential (primary, idiopathic) hypertension (with the belief that an increase in blood pressure in these individuals was essential to maintain adequate

perfusion of vital organs). Undoubtedly this group represents a spectrum of diseases and includes identified types of secondary hypertension.

Heredity: Genetic factors have a role to play in the causation of hypertension as shown by animal and human population studies. Most studies suggest that inheritance is probably multifactorial. Environmental factors such as increased salt intake, obesity, occupation (sedentary habits), family size and crowding may be important in the development of hypertension.

Other contributory factors: Age, race, sex, cigarette smoking, serum cholesterol, glucose intolerance, weight and perhaps plasma renin activity are factors which modify the course of essential hypertension.

3.2 Normal Regulation of Blood Pressure

A brief review of the physiology and pathophysiology of blood pressure regulation is essential in order to understand the pharmacology of anti-hypertensive drugs.

Arterial pressure is under tight control that is constantly maintained even during stress. Arterial pressure is equal to the product of cardiac output and peripheral resistance, the reflex mechanisms responsible for control of blood pressure operate by altering one or both of the variables.

BP = TPR x CO
Where;
BP = Blood pressure, TPR = Total peripheral resistance, CO = cardiac output.

In hypertension, where the arterial pressure is controlled at too high a level, drugs are aimed at modifying control mechanisms to allow pressure to reduce to normal. The control of peripheral resistance occurs at the arterioles, the control of cardiac output is an interplay of cardiac function and extra cardiac determinants of venous return, which are venous capacitance and blood volume.

3.3 Non Pharmacological Intervention

i. Relief of stress (where identifiable)
ii. Diet low in saturated fat
iii Restriction of sodium intake
iv. Weight loss
v. reduction of alcohol intake
vi. Caesation of smoking

vii. Regular exercise
viii. Behavioural modification

3.4 Basic Pharmacology of Antihypertensive Agents

Considerable progress has been made in the treatment of hypertension with the advent of newer drugs. Some of the newer agents have better therapeutic potentials and better patient compliance than the previous drugs. For mild forms of hypertension, tranquilizers and or diuretics without sodium restriction are the first choice of drugs. In the case of mild to moderate forms of hypertension, beta blockers such as propranolol with thiazide diuretics or labetalol (alpha and beta blockers) or prazosin remain as agents of monotherapy. For moderate forms of hypertension, centrally acting agents such as alpha methyldopa and clonidine given alone or together with a diuretic appear to be most effective in the majority of patients. Prazosin (an alpha blocker and vasodilator) with a diuretic has been shown to produce a better response in many cases of moderate hypertension. In moderate to refractory forms, hydralazine with a beta blocker and a diuretic can be used.

Recently, it has been shown that the angiotensin converting enzyme inhibitor, captopril, when given with frusemide is effective in refractory cases and has a better benefit to risk ratio.

In hypertensive emergencies drugs such as diazoxide (a non-diuretic thiazide) are administered as a bolus intravenously or sodium nitroprusside is given by intravenous infusion to reduce elevated blood pressure.

All antihypertensive agents act at one or more of the four anatomic control sites which are the heart, arteries, veins and the kidneys. A useful classification of these principal regulatory site or mechanism on which they act. Because of their common mechanisms of action, drugs within each category produce a similar spectrum of toxicity. The categories are:

1. Diuretics - lower blood pressure by depleting the body of sodium and reducing blood volume.
2. Sympathoplegic agent - lowers blood pressure by reducing peripheral vascular resistance inhibiting cardiac function and increasing venous pooling in capacitance vessels. Some of them reduce cardiac output.
3. Direct vasodilators: which reduce pressure by relaxing vascular smooth muscle thus dilating resistance vessels and to varying degree also increasing capacitance.

4. Angiotensin Converting Enzyme Inhibitors: they reduce peripheral vascular resistance and (potentially) blood volume.

The fact that these drug groups act by different mechanism allows the combination of two more groups with increased efficacy and in some cases decrease toxicity.

Adapted from: Laragh, J.H et al: The Renin Axis and vasoconstriction volume.

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3.5 Drugs Altering Sodium and Water Balance (Diuretics) and Centrally Acting Sympathoplegic

Dietary sodium restriction has been known for many years to decrease blood pressure in hypertensive patients. With the advent of diuretics, sodium restriction was thought to be less important. Now there is general agreement that dietary control of blood pressure is relatively nontoxic therapeutic measure and may even be preventive. Several studies have shown that modest dietary sodium restriction lowers blood pressure in many hypertensive individuals.

Diuretics: Diuretics are employed in mild to moderate hypertensive cases and serve as important adjuncts to more potent agents in the management of patients with moderate to severe hypertension. The useful drug interactions between diuretics and non-diuretics (synergism) have valuable clinical advantages. These include the reduction of the antihypertensive drug dosage requirements, made possible by the decrease in dose-related adverse reactions. Several sympathetic depressants (reserpine, guanethidine, methyldopa) and vasodilators (hydralazine, nitroprusside) have the property of causing sodium and water retention. Examples of diuretics are thazides:- hydrochlorothiazide (Esidrex). Loop diuretics: frusemide, ethacrynic acid; others spironolactone (Aldactone), triamterene.
Centrally Acting Sympathoplegic Drugs
Alpha methyldopa (Aldomet)

The antihypertensive action of methyldopa is on the central nervous system as evidenced by the antagonism by the decarboxylase inhibitors penetrating the central nervous system. The action is due to the metabolic product of methyldopa, known as alpha methyl - norepinephrine which stimulates alpha adrenergic receptors. The peripheral action of

methyldopa also contributes to its antihypertensive effect giving a reduction in renal vascular resistance, direct peripheral vasodilation and some reduction in plasma renin activity. Side effects include sedation, tight sleep, increased rapid eye movement (REM) sleep, edema, positive Coombs test and occasional haemolytic anemia. Methyldopa is available as enteric coated tablet 250mg, 500mg. It is also available in 250mg solution for parenteral administration with maximum dosage in 24 hours between 2 to 3g.

3.6 Vasodilators e.g. Hydralazine (Apresoline)

Hydralazine lowers peripheral vascular resistance and reduces blood pressure with an increase in cardiac output by the baroreceptor reflex mechanism. It directly dilates arterioles by relaxing the arterial smooth muscle. The baroreceptor effect induces an increase in stoke volume and heart rate, together with an increase in myocardial oxygen consumption. This necessitates the administration of drug e.g. beta blockers to counteract the cardiac effects. The hypotensive effect of hydralazine is greatly enhanced by the addition of a diuretic or propranolol.

Other vasodilators are minoxidil (Loniten), diazoxide (Hyperstat).

Renin Angiotensin Converting Enzyme Inhibitors
Captopril: It is the first orally effective inhibitor of angiotensin converting enzymes. In mild to moderate hypertension, captopril is very effective and in severe forms captopril alone or with a diuretic and/or a beta blocker usually reduces blood pressure more effectively than standard triple therapy (hydralazine 200mg + propranolol 320mg + hydrochlorothiazide 100mg).

At present patients not responding to or not tolerating the traditional antihypertensive therapy are the most suitable patients for captopril treatment.

L **THE RENIN -ANGIOTENSIN - ALDOSTERONE HORMONAL SYSTEM AND CONTROL OF BLOOD PRESSURE VIA VASOCONSTRICTION AND BLOOD VOLUME**

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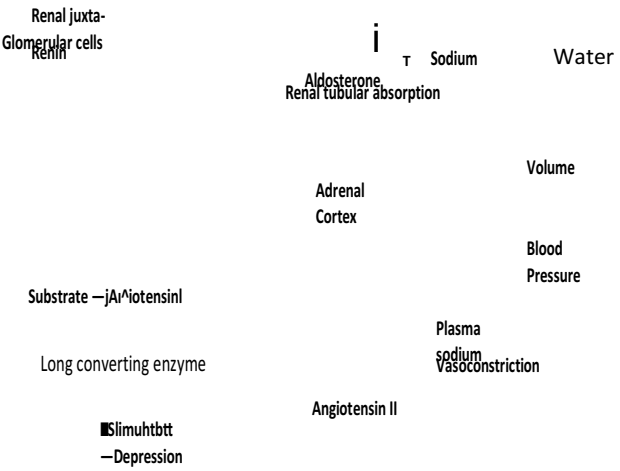

3.7 Beta Adrenergic Blockers

Beta blockers are divided into 3 groups:

1. Drugs without, selectivity e.g. alprenolol, pindolol propranolol
2. Cardio-selective drugs e.g. Atenolol, metroprololol, practolon
3. Drugs with alpha adrenoceptor activity.
4. Propranolol being the most common of the group will be discussed.

Propranolol is the drug of choice in many hypertensive cases. Renin release by the kidney is partially under beta adrenergic control and propranolol therapy reduces plasma renin level at relatively low doses, and particularly decreases the elevation in renin activity that occurs with standing or during exercise, e.g. propranolol is most successful in reducing blood pressure in patients with normal renin essential hypertension in the dose range of 50mg to 320mg per day. However, in patients with low renin activity, it exerts its antihypertensive effect at doses of 100 to 200mg it.

Suggested mechanisms of action include a reduction in plasma renin activity, a reduction in cardiac output, the blockade of peripheral adrenergic neurons and interference with baroreceptor.

3.8 Alpha Adrenergic Blockers

Examples of alpha adrenergic blockers are phenoxybenzamine and phentolamine. Their actions are similar to those of vasodilators in that they also cause a reflex increase in heart rate and contractile force, and an increase in plasma renin activity. The alpha blockers prevent vasoconstriction in both vascular beds. Postural hypertension and erratic oral absorption limit the usefulness of phenoxybenzamine and phentolamine in the treatment of essential hypertension.

Calcium Channel Blockers

Calcium channel blockers have anti-anginal, antiarrhythmic properties as well as antihypertensive properties. They dilate peripheral arteries and reduce blood pressure. Verapamil, diltiazem, amlodipine, nicardipine and nifedipine are examples of calcium channel blockers antihypertensive of choice considering haemodynamic and pharmacokinetic characteristics.

3.9 Management of Hypertensive Emergencies and Hypertensive Urgencies

Hypertensive emergencies require immediate hospitalization and administration of parenteral antihypertensive medications to reduce arterial pressure. Effective therapy improves prognosis, arrests the progression of end-organ damage and reverses symptoms. Usually, treatment reverses the vascular changes in the eye and slows down renal damage. The crisis situation will determine the antihypertensives of choice, considering hemodynamic and pharmacokinetic characteristics. If acute left ventricular failure or other serious conditions are involved, antihypertensives like nitroprusside, diazoxide, trimethophan and labetalol may be used immediately.

In hypertensive urgencies oral antihypertensive loading regimens may be appropriate. Captopril, minoxidil, clonidine, and prazosin have been used to lower blood pressure in hypertensive urgencies.

SELF ASSESSMENT EXERCISE

1. Discuss the calcium channel blockers and their mechanism of action in the treatment of hypertension.

Calcium channel blockers have…. .....and .....properties.

Mechanisms of action.

They dilate ..... They inhibit

2. Non pharmacologic intervention in the treatment of hypertension. **4.0 CONCLUSION**

Clinical presentation of the patient will determine the rate of blood pressure lowering. This should be individualized as ischemic damage to the heart and brain can occur following very rapid fall in blood pressure. In general, gradual lowering of blood pressure (5 to 10mmHg) every five to ten minutes is recommended in patients with hypertension.

5.0 SUMMARY

Pharmacological classifications of common antihypertensives are:

- Sympathoplegic agents e.g. Methyldopa, clonidine.
- Beta receptor blockers e.g. propranolol, pindolol.
- Vasodilators e.g. hydralazine, diazoxide, nitroprusside.
- Angiotensin converting enzyme inhibitors e.g. captopril, enalapril, lisinopril
- Calcium channel blockers e.g. nifedipine, verapamil
- Diuretics e.g. frusemide, spironolactone.

Two fundamental variables that determine blood pressure is the cardiac output and the total peripheral resistance. Arterial pressure= Cardiac output x peripheral resistance

ANSWER TO SELF ASSESSMENT EXERCISE

1. Calcium channel blockers have antianginal, antiarrhythmic and antihypertensive properties. Examples are verapmil, diltiazem, amlodipine, nicardipine and nifedipine.
   Mechanisms of action
   They dilate peripheral arterioles and reduce blood pleasure. They also inhibit calcium influx into the arterial smooth muscle cells thereby reducing the blood pressure in the arteries.

2. Non pharmacologic intervention in the treatment of hypertension

   a. Relief of stress
   b. Diet low in saturated fat
   c. Restriction of sodium intake
   d. Weight loss
   e. Reduction of alcohol intake
   f. Ceasation of smoking
   g. Regular Exercise
   h. Behaviour modification

6.0 TUTOR-MARKED ASSIGNMENT

Explain by giving examples, the categories of drugs used in the treatment of hypertension.

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MODULE 4 CHEMOTHERAPEUTIC AGENTS

Unit 1 Chloramphenicol, Tetracyclines
Unit 2 Sulphonamides, Trimethoprim and Quinolones
Unit 3 Beta-Lactam Antibiotics and other Inhibitors of Cell Wall Synthesis
Unit 4 Antiviral Agents
Unit 5 Antifungal Agents
Unit 5 Chemotherapy of Cancer

UNIT 1 CHLORAMPHENICOL, TETRACYCLINES

CONTENTS

1.0 INTRODUCTION

Chloramphenicol is a potent inhibitor of microbial protein synthesis by binding to and interfering with their ribosomes. It is soluble in alcohol but poorly soluble in water. Chloramphenicol succinate, which is used for parenteral administration, is highly water-soluble. It is hydrolyzed *in vivo* with liberation of free chloramphenicol.

2.0 OBJECTIVES

At the end of the unit the learner will understand the;

- pharmacokinetics and clinical uses of chloramphenicol
- pharmacokinetics and clinical uses of tetracyclines
- adverse reactions of chloramphenicol and tetracyclines.

3.0 MAIN CONTENT

3.1 Chloramphenicol: Description and Mechanism of Action

It is a potent inhibitor of microbial protein synthesis. It binds reversibly to the 50s subunit of the bacterial ribosome. It inhibits the peptidyl transferase step of protein synthesis. Chloramphenicol is active against both aerobic and anaerobic gram positive and gram-negative organisms. It is active against rickettsiae but not chlamydiae. Most gram-positive bacteria are inhibited at concentrations of l-10µg/ml, and many gramnegative bacteria are inhibited by concentrations of 0.2-5µg/ml. *Haemophilus Influenzae, Neisseria meningitides,* and some strains of bacteroides are highly susceptible and for them chloramphenicol may be bactericidal.

3.2 Pharmacokinetics

The usual dosage of chloramphenicol is 50-100mg/kg/d. After oral administration, crystalline chloramphenicol is rapidly and completely absorbed. A 1g oral dose produces blood levels between 10 and 15a/ml. Chloramphenicol palmitate is a prodrug that is hydrolyzed in the intestine to yield free chloramphenicol. The parenteral formulation, as chloramphenicol succinate, yields free chloramphenicol by hydrolysis, giving blood levels somewhat lower than those achieved with orally administered drug. After absorption, chloramphenicol is widely distributed to virtually all tissues and body fluids, including the central nervous system and cerebrospinal fluid such that the concentration of chloramphenicol in brain tissue may be equal to that in serum. The drug penetrates cell membrane readily.

3.3 Clinical Uses

Chloramphenicol is no longer used as a systemic drug because of availability of other effective drugs (e.g. cephalosporins), potential toxicity, bacterial resistance for treatment of severe rickettsial infections, such as typhus, or Rock Mountain spotted fever, in children for whom tetracyclines are contraindicated, i.e. those under 8 years of age. It is an alternative to a β-lactam antibiotic for treatment of meningococcal meningitis occurring in patients who have major hypersensitivity reactions to penicillin or bacterial meningitis caused by penicillin resistant strains of pneumococci. The dosage is 50-100mg/kg/d in four divided doses. Chloramphenicol is occasionally used topically in the treatment of eye infections.

3.4 Adverse Reactions of Chloramphenicol

1. **Gastrointestinal disturbances:** Adults occasionally develop nausea, vomiting, and diarrhoea. It is rare in children. Oral or vaginal candidiasis may also occur.

2. **Bone marrow disturbance:** Chloramphenicol commonly causes a dose-related reversible suppression of red cell production at dosage exceeding 50mg/ kg/d after 1- 2 weeks. Aplastic anemia is a rare consequence of chloramphenicol administration by any route. It is idiosyncratic reaction unrelated to dose, though it occurs more frequently with prolonged use. It is irreversible and can be fatal. Aplastic anemia probably develops in one of every 24,000-40,000 patients who have taken chloramphenicol.

3. **Toxicity for newborn infants:** Newborn infants lack an effective glucoronic acid conjugation mechanism for the degradation and detoxification of chloramphenicol. When infants are given dosages above 50mg/kg/d the drug may accumulate resulting in the gray baby syndrome, with vomiting, flaccidity, hypothermia, gray colour, shock and collapse.

4. **Interaction with other drugs:** Chloramphenicol inhibits hepatic microsomal enzymes that metabolize several drugs. Half-lives are prolonged, and the serum concentration of phenytoin, tolbutamide, chlorpropamide, and warfarin are increased. Chloramphenicol can antagonize antibacterial drugs such as penicillins or aminoglycoside.

3.5 Tetracyclines: Description and Mechanism of Action

They are crystalline amphoteric substances of low solubility. They occur as hydrochlorides which are more soluble. Tetracyclines hydrochloride solutions are fairly stable except chlortetracycline. Tetracyclines chelate divalent metal ions which can interfere with their absorption and activity.

They are broad spectrum bacteriostatic antibiotics that inhibit protein synthesis. They are active against many gram-positive bacteria, including anaerobic, rickettsiae, chlamydiae, mycoplasmas and L-forms: and against some protozoa e.g. amoebas. The antibacterial activities of most tetracyclines are similar except strains may remain susceptible to doxycycline or minocycline, drugs that are less rapidly transported by the pump that is responsible for resistance. Tetracyclines enter microorganisms in part by passive diffusion and in part by an energy dependent process of active transport.

3.6 Pharmacokinetics of Tetracyclines

Absorption after oral administration is approximately 30% for chlortetracycline, 60-70% for tetracycline, oxytetracycline, demeclocycline, and 95-100% for doxycycline and methacycline. A portion of an orally administered dose of tetracycline remains in the gut lumen modifies intestinal flora and is excreted in the faeces. Absorption occurs mainly in the upper small intestine and is impaired by food (except doxycycline and minocycline); by divalent cations (Ca^{2+}, Mg^{2+}, Fe^{2+}) or Al^{3+}, by dairy products and antacids which contain multivalent cations, and by alkaline pH. Specially buffered tetracycline solutions are formulated for intravenous administration. Tetracyclines are 40-80% bound by serum proteins. Oral dosages of 500mg every 6 hours of tetracycline hydrochloride or oxytetracycline produce peak blood levels of 4-6 µg/ml, 200mg dose of doxycycline or minocycline peak levels of2-4 µg/ml are achieved with a.

3.7 Clinical Uses

Tetracycline is the drug of choice in infections with *mycoplasma pneumoniae*. *Chlamydiae, rickettsiae,* and some spirochaetes. They are used in combination regimens to treat gastric and duodenal ulcer disease caused by *Helicobacter pylori.* They can be used in various gram positive and gram negative bacterial infections, vibrio infections, if the organism is not resistant. In cholera, tetracyclines rapidly stop the shedding of vibrios but resistance has appeared during epidemics. Tetracycline is effective in sexually transmitted diseases. Tetracyclines are used in the treatment of protozoal infections, e.g those due to *Entamoeba histolytica or Plasmodium falciparum.* It is used in the treatment of acne, exacerbation of bronchitis, community acquired pneumonia, lyme disease, relapsing fever, leptospirosis and some non tuberculous mycobacterial infections.

The oral dose for rapidly excreted tetracyclines, equivalent to tetracycline hydrochloride is 0.25 - 0.5g four times daily for adults and 20-40mg/kg for children (8 years of age and older). For severe systemic infections, the higher dosage is indicated at least for the first few days.

3.8 Adverse Reactions of Tetracyclines

Are gastrointestinal i.e. nausea, vomiting and diarrhoea. Bony structures and teeth because they are readily bound to calcium deposited in newly formed bone or teeth and this can cause discoloration of teeth. It can cause liver toxicity, kidney toxicity. Intravenous injection can cause venous thrombosis. Intramuscular injection can cause painful local irritation and should be avoided.

SELF ASSESSMENT EXERCISE

1. State the adverse reactions of chloramphenicol.

A .....
B ..... .
C .....
D .....

2. What are the uses of tetracycline?

A ....
B .....
C .....

D .....

E.....
F.....

4.0 CONCLUSION

Tetracyclines are broad-spectrum bacteriostatic antibiotics that inhibit protein synthesis. Chloramphenicol is also a broad spectrum bacteriostatic antibiotic that inhibits protein synthesis.

5.0 SUMMARY

Tetracyclines and chloramphenicol are bacteriostatic antibiotics. They are active against gram positive and gram negative bacteria, aerobes and nonaerobic. They have similar uses but because of potential toxicity, bacterial resistance and availability of other effective antibiotics like (cephalosporins), chloramphenicol has become an obsolete systemic drug.

ANSWER TO SELF ASSESSMENT EXERCISE

1. Adverse reactions to chloramphenicol

a. Gastrointestinal disturbances e.g. nausea, vomiting and diarrhoea.
b. Bone marrow disturbance e.g. aplastic anaemia
c. Toxicity for newborn infants e.g. gray baby syndrome
d. Interaction with other drugs e.g. can antagonize bactericidal drugs like ampicillin or gentamycin.

2. Uses of Tetracycline

a) Infections with *Mycoplasm pneumonia, Chyamdiae rickettsial* and spirochetes can be treated with tetracycline
b) To treat gastric and duodenal ulcer disease caused by *Helicobacter pylori.*
c) Various gram positive and gram negative bacterial, infections can be treated with tetracycline.
d) Cholera and sexually transmitted diseases can be treated with tetracycline
e) Protozoa infections due to *Entamoeba histolytica or plasmodium falciparum* can be treated with tetracycline
f) Acne, Pneumonia, bronchitis, relapsing fever can be treated with tetracycline.

6.0 TUTOR-MARKED ASSIGNMENT

Discuss the clinical uses and adverse reactions to chloramphenicol.

7.0 REFERENCES/FURTHER READINGS

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UNIT 2 SULPHONAMIDES, TRIMETHOPRIM AND QUINOLONES

CONTENTS

1.0 INTRODUCTION

The basic formula of the sulfonamides and its structure is similar to that of para-amino benzoic acid (PABA). Sulfonamides are more soluble at alkaline than at acid pH. Most of them can be prepared as sodium salt, which are used for intravenous administration.

Sulfonamides can be divided into three major groups:

(1) Oral, absorbable;
(2) Oral nonabsorbable
(3) Topical

Trimethoprim, a trimethoxy benzyl pyrimidine, inhibits bacterial dihydrofolic acid reductase about 50,000 times more efficiently than the same enzyme of mammalian cells.

2.0 OBJECTIVES

At the end of the unit the learner would know:
- pharmacokinetics and clinical uses of sulphonamides and trimethoprim
- pharmacokinetics and clinical uses of quinolones
- adverse reactions of sulphonamides, trimethoprim and quinolones.

3.0 MAIN CONTENT

3.1 Sulfonamides and Trimethoprim

Mechanisms of action of Sulfonamides: They inhibit growth by reversibly blocking folic acid synthesis. Sulfonamides inhibit both gram-positive and gram-negative bacteria, *nocardia, Chlamydia trachomatis* and some enteric bacteria such as *E coli, Klebsiella, Salmonella, Shigella and Enterobacter,* are inhibited. Interestingly, rickettsial are not inhibited by sulfonamides but are stimulated in their growth. Sodium salts of sulfonamides in 5% dextrose in water can be given intravenously, but except for sulfamethoxazole-trimethroprim combinations, which are rarely used. The oral, absorbable sulfonamides can be classified as short, medium or long acting on the basis of their half-lives. They are absorbed from the stomach and small intestine and distributed widely to tissues and body fluids (including the central nervous system and cerebrospinal fluid), placenta and fetus. Absorbed sulfonamides become bound to serum proteins to an extent varying from 20% to over 90%.

Therapeutic concentrations are in the range of 40 - 100 mg/ml of blood. Peak blood levels general occur 2-6 hours after oral administration.

Trimethoprim pharmacokinetics: Trimethoprim is usually given orally, alone or in combination with sulfamethoxazole, the latter chosen because it has a similar half-life. Trimethoprim- sulfamethoxazole can also be given intravenously.

Trimethoprim is absorbed efficiently from the gut and distributed widely in body fluids and tissues, including cerebrospinal fluids. Because trimethoprim is more lipid-soluble than sulfamethoxazole, it has a larger volume of distribution than the latter drug. When 1 part of trimethoprim is given with 5 parts of sulfamethoxazole (the ratio in the formulation), the peak plasma concentrations are in the ratio 1:20, which is optimal for the combined effects of these drugs in vitro. About 65-70% of each participant drug is protein bound, and 30-50% of the sulfonamide and 50-60% of the trimethoprim are excreted in the urine within 24hours. The dose should be reduced by half for patients with creatinine clearances of 15 to 30 ml/min. Trimethoprim has more antibacterial activity in prostatic and vaginal fluids than many other antimicrobial drugs.

Clinical uses of Sulphonamides

Sulphonamides are infrequently used as single agents. They were formerly the drugs of choice for infections such as *Pneumocystitis jirovecii* (formerly *P. carinii)* pneumonia, toxoplasmosis, norcadiosis and occasionally other bacterial infections.They have been largely supplanted by the fixed drug combination of trimethoprim sulfamethoxazole (e.g septrim®). Many strains of formerly susceptible species, including *meningococci, pneumococci, streptococci, staphylococci and gonococci* are now resistant. Sulfonamides can be useful for the treatment of urinary tract infections due to susceptible organisms and in other special clinical situations.

(a) Oral absorbable agents: sulfisoxazole and sulfamethoxazole are short to medium acting agents that are used exclusively to treat urinary tract infections. The usual adult dosage is 1g of sulfisoxazole four times daily or 1g of sulfamethoxazole two or three times daily
(b) Oral non absorbable agent: sulfasalazine (salicylazosul fapyridine) is widely used in ulcerative colitis enteritis and other inflammatory bowel disease.
(c) Topical agents: Sodium sulfacetamide ophthalmic solution or ointment is effective treatment for bacterial conjunctivitis and as adjunctive therapy for trachoma.

Clinical uses of Trimethoprim:

(a) Trimethoprim can be given alone (lOOmg twice daily) in acute urinary tract infection (oral trimethoprim)
(b) Oral trimethoprim-sulphamethoxazole e.g. (oral septrim®): A combination of trimethoprim-sulfamethoxazole is effective treatment for *P. jiroveci* pneumonia, shigellosis, systematic salmonella infections (caused by ampicillin or chloramphenicol resistant organisms), complicated urinary tract infections, prostatitis, some non-tuberculosis mycobacterial infections, and many others. It is active against many respiratory tract pathogens including the *pneumoccocus haemophilus* species, *Moraxella catarrhalis,* and *Klebsiella pneumoniae* (but not *Mycoplasma pneumoniael),* making it a potentially useful alternative to B- lactam drugs for treatment of upper respiratory tract infections. Two double strength tablets (trimethoprim 160 mg plus sulfamethoxazole 800g) given every 12 hours is effective treatment for urinary tract infections and prostatitis.
(c) Intravenous trimethoprim sulfamethoxazole solution of the mixture containing 80mg trimethoprim plus 400mg sulfamethoxazole per 5ml diluted in 125ml of 5% dextrose in water can be administered by intravenous injection over 60-90 minutes. It is used to treat moderately severe to severe pneumocystis pneumonia.
(d) Oral pyrimethamines with sulfonamide pyrimethamine and sulfadiazine have been used for treatment of leishmaniasis and toxoplasmosis. In falciparum malaria, the combination of pyrimethamine with sulfadoxine (fansidar®) has been employed. Adverse reactions of Sulphonamide and Trimethoprim.

Sulfonamides and their derivatives are cross allergenic. The most common adverse effects are fever, skin rashes, exfoliative dermatitis, photosensitivity, urticarial, hematuria, Stevens-Johnson syndrome, although less uncommon, stomatitis, conjunctivitis, arthritis, hematopoetic disturbances, hepatitis and rarely polyarthritis nodosa and psychosis.

The adverse reactions of trimethoprim are megaloblastic anaemia, leukopenia, and granulocytopenia, nausea, vomiting, drug fever, vasculitis, renal damage and CNS disturbance occasionally occur. Patients suffering from AIDS and Pneumocystis pneumonia have a particularly high frequency of untoward reactions to trimethoprim-sulfamethoxazole especially fever, rashes, leukopenia, diarrhoea, elevations of hepatic amino transferases, hyperkalemia, hyponatremia.

3.2 Fluoroquinolones

Description and Mechanism of action: They are active against a variety of gram-positive and gram-negative bacteria. Fluoroquinolones were originally developed because of their excellent activity against gram negative aerobic bacteria; they had limited activity against gram positive organisms. Several newer agents have improved activity against gram positive cocci. Norfloxacin is the least active of the fluoroquinolones against both gram-negative and gram-positive organisms. Ciprofloxacin, enofloxacin, ofloxacin and perfloxacin comprise a second group of similar agents possessing excellent gram-negative activity and

moderate to good activity against gram-positive bacteria. Quinolones block bacterial DNA synthesis by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV. Inhibition of DNA gyrase prevents the relaxation of positively supercoiled DNA that is required for normal transcription and replication.

Inhibition of topoisomerase IV interferes with separation of replicated chromosomal DNA into the respective daughter cells during cell division.

3.3 Pharmacokinetics

After oral administration, the fluoroquinolones are well absorbed (bioavailability of 80-95%) and distributed widely in body fluids and tissues. Serum half-lives range from 3 hours (norfloxacin and ciprofloxacin) up to 10 (perfloxacin and fleroxacin) or longer (sparfloxacin). The relatively long half-lives of levofloxacin, moxifloxacin, sparfloxacin and trovofloxacin permit once-daily dosing. The pharmacokinetics of ofloxacin and levofloxacin are identical. Oral absorption is disturbed by divalent cation including those in antacids. Serum concentrations of intravenously administered drugs are similar to those of orally administered drugs. Most fluoroquinolones are eliminated by renal mechanisms, either tubular secretion or glomerular filtration.

3.4 Clinical Uses of Fluoroquinolones

Fluoroquinolones are effective in urinary tract infections even when caused by multidrug - resistant bacteria e.g. *pseudomonas.* Norfloxacin, 400mg, ciprofloxacin 500mg and ofloxacin 400mg given orally twice daily are all effective. These agents are also effective for bacterial diarrhoea caused by *shigella, salmonella,* toxigenic *E. coli* or *Campylobacters.* Fluoroquninolones (except norfloxacin, which does not achieve adequate systemic concentrations) have been employed in infections of soft tissues, bones and joints and in intra- abdominal and respiratory tract infections, including those caused by multidrug resistance organisms such as *pseudomonas* and *enterobacter.* Ciprofloxacin and ofloxacin are effective for gonococci infection, ciprofloxacin is occasionally used for treatment of tuberculosis and atypical mycobacterial infections. Fluoroquinolones have not been routinely recommended for the treatment of pneumonia and other upper respiratory tract infections.

3.5 Adverse Reactions of Fluoroquinolones

Fluoroquinolones are extremely well tolerated. The most common effects are nausea, vomiting, and diarrhoea. Occasionally, headache, dizziness, insomnia, skin rash, abnormal liver function develop. Sparfloxacin may prolong QT interval. Fluoroquinolones may damage growing cartilage and cause an arthropathy, thus, they are not routinely recommended for use in patients under 18 years of age.

SELF ASSESSMENT EXERCISE

1. What are the mechanism of Action and Clinical Uses of Sulfonamides?

(a) Mechanism of action .....
.....

(b) Uses of Sulfonamides

i. .....
ii. .....

iii. .....95.....

iv. .....

2. (a) What are the clinical uses of Fluoroquinolones
i .....
ii .....
iii.....
iv.....

(b) State the adverse reaction of Fluoroquinolones.
i. .....

ii. .....

iii. .....

iv. .....

4.0 CONCLUSION

Sulfonamides are not frequently used as single agents. They are now usually combined as trimethoprim-sulfamethoxazole. They are used for infections caused by *Pneumocystitis jirovecii,* pneumonia, toxoplasmosis, and norcardiosis. Fluoroquinolones are active against gram positive and gram negative organisms.

5.0 SUMMARY

Sulfonamides can be classified as oral absorbable, oral non absorbable or topical. They are useful for the treatment of urinary tract infections, ulcerative colitis, and enteritis and as ophthalmic solution to the eye. The fluoroquinolones are active against gram positive and gram negative bacteria. They are useful in urinary tract infections, bacterial diarrhoea, soft tissues, bones and joints, intra-abdominal and respiratory tract infections.

ANSWER TO SELF ASSESSMENT EXERCISE

1. Mechanism of action of sulfonamides. They inhibit growth by reversibly blocking folic acid synthesis.

They inhibit both gram positive and gram negative bacteria, *Nocardia, Chlamydia trachomatis,* and some protozoa.

b) Uses of Sulfonamides

(a) Sulfonamide combination is used in treating malaria e.g. pyrimethamine and sulfadoxine
(b) Urinary tract infections
(c) Ulcerative colitis, enteritis, and other inflammatory bowel disease
(d) Sodium sulfonamide ophthalmic solution or ointment is effective treatment for bacterial conjunctivitis and as adjunctive therapy for trachoma.

2. (a) Clinical uses of Fluoroquinolones

a. Urinary tract infections
b. Bacterial diarrhoea caused by *Shigella, Salmonella*
c. Soft tissues e.g. bones, joints, intra-abdominal and respiratory tract infections.
d. Tuberculosis...

(b) Adverse reactions of Fluoroquinolones

i. Nausea, vomiting
ii. Headache, dizziness
iii. Skin rash
iv. Insomnia

6.0 TUTOR-MARKED ASSIGNMENT

What are the clinical uses and adverse reactions of fluoroquinolones.

7.0 REFERENCES/FURTHER READINGS

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UNIT 3 BETA-LACTAM ANTIBIOTICS AND OTHER INHIBITORS OF CELL WALL SYNTHESIS

CONTENTS

1.0 INTRODUCTION

The penicillins are classified as β- Lactam drugs because of their unique four-membered lactam ring. They share features of chemistry, mechanism of action, pharmacological and clinical effect and immunologic characteristics with cephalosprins, monobactams, carbapenems, and β-Lactamase inhibitors, which also are β-Lactam compound. All penicillins have the basic structure.

They possess a thiazolidine ring (A) attached to a β-Lactam ring (B) that carries a secondary amino group (RNH-). Structural integrity of the 6-amino penicillanic acid nucleus is essential for the biological activity of these compounds. If the β-Lactam ring is enzymatically cleaved by bacterial β - Lactamases, the resulting product, penicilloic acid, lacks antibacterial activity.

2.0 OBJECTIVES

At the end of the unit the learner will know:
- the mechanism of action of penicillins and cephalosporins
- clinical uses of penicillins and cephalosporins
- pharmacokinetics of penicillins and cephalosporins.

3.0 MAIN CONTENT

3.1 Classification of Penicillin

The attachment of different substituents to 6-amino penicillanic acid determines the essential pharmacologic and antibacterial properties of the resulting molecules.

Penicillins are classified into three.

(1) Penicillins (e.g. Penicillin G): They have the greatest activity against gram-positive organism, gram-negative cocci, and non β- lactamases producing anaerobes. They have little activity against gram-negative rods. They are susceptible to hydrolysis by β- Lactamases.
(2) Anti-staphylococcal penicillins (e.g. nafcillin) they are resistant to Staphylococci β - lactamases. They are active against Staphylococci and streptococci but inactive against enterococci, anaerobic bacteria and gram-negative cocci and rods.

Extended-spectrum penicillins (ampicillin and the anti-pseudomonal penicillins). These drugs retain the antibacterial spectrum of penicillin and have improved activity against gram-negative organism but they are destroyed by β-lactamases.

3.2 Mechanism of action

Penicillins inhibit bacterial growth by interfering with a specific step in bacterial cell wall synthesis. The cell wall is a rigid outer layer that is not found in animal cells. It completely surrounds the cytoplasmic membrane maintaining the shape of the cell and preventing cell lysis from high osmotic pressure. The cell wall is composed of a complex cross-linked polymer, peptidoglycan (murein, mucopeptide). The polysaccharide contains alternating amino sugars, N-acetyl glucosamine and N-acetylmuramic acid. A five amino-acid peptide is linked to the N- acetylmuramic acid sugar. The exact mechanism responsible for cell death is not completely understood but autolysins, bacterial enzymes that remodel and break down cell wall, are involved. Penicillins and cephalosporins are bactericidal only if cells are actively growing and synthesizing cell wall.

3.3 Pharmacokinetics

Absorption of orally administered drug differs greatly for different penicillins, depending in part on their acid stability and protein binding. Methicillin is acid labile and gastro intestinal absorption of nafcillin is erratic, so neither is suitable for oral administration. Dicloxacillin, ampicillins are acid stable and relatively well absorbed producing serum concentration in the range of 4-8 µg/ml following 500mg oral dose. Absorption of most oral penicillins (amoxicillin being an exception) is impaired by food, and the drugs should be administered at least 1-2 hours before or after a meal.

After parenteral administration absorption of most penicillin is complete and rapid. Administration by the intravenous route is preferred because of irritation and local pain produced by the intramuscular injection of large doses. Serum concentrations 30 minutes after an intravenous injection of 1g of penicillin (equivalent to approximately 1.6 million units of penicillin G) are 20-50 µg/ml. Only a fraction of the total drug in serum is present as free drug, the concentration of which is determined by protein binding. Highly protein-bound penicillins (e.g. nafcillin) produce lower levels of free drug in serum than less protein bound penicillins (e.g. penicillin G, ampicillin). Protein binding becomes clinically relevant, when the protein-bound fraction is approximately 95% or more. Penicillins are widely distributed in body fluids and tissues with few exceptions. They are polar molecules, and the concentration within cells is less than in extracellular fluids. Benzanthine and procaine penicillins are formulated to delay absorption, resulting in prolonged blood and tissue concentrations. Penicillin concentrations in most tissues are equal to those in serum. It is excreted into sputum and milk to levels 3-15% of those present in the serum. Penetration into the eye, the prostate, and the CNS is poor.

3.4 Clinical Uses

Penicillins G is the drug of choice for infections caused by *streptococci, meningococci, enterococci,* penicillin susceptible *pneumococci,* non β-Lactamase producing *staphylococci, Treponema pallidium* and many other spirochetes, *Clostridium* species, *actinomyces* and other gram positive rods and non β-Lactamase producing gram negative anaerobic organisms.

Penicillin G (IV) Adult Dose is l-4mEq 4-6h, Cloxacillin 250mg - 500mg 4-6hr, Nafcillin IV 1-2g 4-6h, Oxacillin IV 1-2every 4-6h, Amoxicillin 250mg - 500mg tid, Amoxicillin/Potassium Clavulinate 500/125 bid, tid Piperacillin IV 3-4g 4-6h,Ticarcillin IV 3g 4-6h
Adverse reactions: Most penicillin are non-toxic, most of the serious adverse effects are due to hypersensitivity.

3.5 Cephalosporin

Cephalosporins are similar to penicillins chemically, in mechanism of action, and in toxicity. Cephalosporins are more stable than penicillins to many bacterial β-Lactamases and therefore usually have a broader spectrum of activity. Cephalosporins are not active against enterococci and *Lesteria monocytogenes*. It has the first, second, third and fourth generation.

First generation: The group includes cefadroxil, cefazolin, cephalotin, cephapirin and cephrodine. These drugs are active against grain-positive cocci, including *pneumococci, streptococci* and *staphylococci, Escherichia coli, Klebsiella pneumoniae* and *Proteus mirabilis* but activity against *P.aeruginosa,* indole-positive proteins, *enterobacter, Serratia marcescens, citrobacter,* and *acinetobacter* is poor. Anaerobic cocci (e.g. *peptococcis, peptostreptococcus)* are usually sensitive, but *B fragilis* is not.
Second generation cephalosporins are cefaclor, cefamandole, cefonicid, cefuroxime, cefproxil, loracarbef and ceforanide. They are active against organisms affected by first generation and in addition they have extended gram negative coverage.

Third generation agents include cefoperazone, cefolaxine, ceftazidime, ceftrizoxime, ceftriaxone, cefixime, cefpodoxime, proxeril, ceditoren, pivoxil, ceftibuten, and moxalactam. The major features of these drugs except (cefoperazone) are their expanded gram-negative coverage and the ability of some to cross the blood-brain barriers. In addition to the gram-negative bacteria inhibited by other cephalosporins, third generations are active against *Citrobacter, Serratia marcescens,* and *providencia* (though resistance can emerge during treatment of infections caused by these species due to selection of mutants that constitutively produce cephalosporinase).

They are also effective against β-Lactamase - producing strains of *haemophilus* and *neisseria.*

Fourth generation cephalosporins: cefepime is an example of a so called fourth-generation cephalosporins. It is more resistant to hydrolysis by chromosomal β-Lactamases (e.g. those produced by enterobacter) and some extended-spectrum β - Lactamases that inactivate many of the third-generation cephalosporins.

It has good activity against *Ps. aeruginosa, Enterobacteriaceace, S. aureus,* and *S. pneumoniae.* It is highly active against *Haemophilus* and *Neisseria.* In animal models of meningitis, it penetrates well into cerebrospinal fluid. It is cleared by the kidneys and has a half-life of 2 hours.

3.5 Adverse Effects of Cephalosporins

Cephalosporins are sensitizing and may elicit a variety of reactions that are identical to those of penicillins i.e. anaphylaxis, fever, skin rashes, nephritis, granulocytopenia, and haemolytic anemia. Some patients that have penicillin allergy may tolerate cephalosporins because the chemical nucleus of cephalosporins is quite different from that of penicillin.

SELF ASSESSMENT EXERCISE

1. Name four different examples of penicillins and state their mechanism of action.

   a. .....
   b. .....
   c. .....
   d. .....

   Mechanism of action

2. State 3 third generation cephalosporins, what are their adverse reactions.

   a. .....
   b. .....
   c. .....
   Adverse reactions of cephalosporins are .....

4.0 CONCLUSION

Antimicrobial agents are of great importance in modern medicine. They can be used for many infections and death threatening diseases using some tablets or capsules or injections.

5.0 SUMMARY

Penicillins are classified into three groups

• Penicillins (e.g. Penicillin G). These have the greatest activity against gram-positive organisms, gram-negative cocci, and non β -Lactamases producing anaerobes.

ANSWER TO SELF ASSESSMENT EXERCISE

1. a. Penicillin G
   b. Oxacillin
   c. Amoxicillin
   d. Ticarcillin

Mechanism of Action: Penicillins inhibit bacterial growth by interfering with a specific step in bacterial cell wall synthesis. Autolysins, bacterial enzymes that remodel and breakdown cell wall are involved.

2. 3 third generation cephalosporins
   a. Cefotaxime
   b. Ceftazidime
   c. Ceftriaxone

Adverse reactions of cephalosporins are anaphylaxis, fever, skin rashes, nephritis, granulocytopenia and haemolytic anemia.

6.0 TUTOR-MARKED ASSIGNMENT

Discuss the first and third generation's cephalosporins.

7.0 REFERENCES/FURTHER READINGS

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UNIT 4 ANTIVIRAL AGENTS

CONTENTS

1.0 INTRODUCTION

Viruses are obligate intracellular parasites. Their replication depends primarily on synthetic processes of the host cell. For antiviral agent to be effective, they must either block viral entry in to or exist from the cell or be active inside the host cell as a corollary. Non-selective inhibitors of virus replication may interfere with host cell function and produce toxicity. Research in antiviral chemotherapy began in the early 1950s, when the search for anticancer drugs generated several new compounds capable of inhibiting viral DNA synthesis. The two first generation antivirals 5- indodeoxyuridine and trifluorothymidine had side effects (i.e. they inhibited hosts cellular as well as viral DNA) that rendered them too toxic for systematic use. However, both are effective when used topically for the treatment of herpes keratitis. Recent research has focused on the identification of agents with greater selectivity, improved stability and lack of toxicity. Selective antiretroviral agents that inhibit critical HIV- 1 enzymes such as reverse transcriptase or the protease required for final packaging of the viral particle have become available. In many viral infections, replication of the virus peaks at or before the manifestation of clinical symptom.

2.0 OBJECTIVES

At the end of the unit the learner will know:
- the agents used in treating viral infections
- the antiretroviral agents used in treating HIV/AIDS.

3.0 MAIN CONTENT

3.1 Agents Used to Treat Herpes Simplex Virus (HSV)& Varicella Zoster Virus (VZV) Infections

Three oral agents used for the treatment of HSV and VZV infections are acyclovir, valacyclovir and famciclovir. They have the same mechanism of action and similar indication for clinical use. They are well tolerated. Acyclovir is the most extensively studied and the only anti-HSV agent available for intravenous use in the United States. Acyclovir is an acyclic guanosine derivative with clinical activity against HSV, HSV-2, and VZV. Viral activity against Epstein-Barr virus, cytomegalovirus and human herpes virus- 6 is present but comparatively weaker. Acyclovir requires three phosphorylation steps for activation. It is converted first to the monophosphate derivative by the virus specific thymidine kinase and then to the di- triphosphate compounds by the host cellular enzymes. Acyclovir triphosphate inhibits viral DNA synthesis by competitive inhibition with deoxy GTP for the viral DNA polymerase, resulting in binding to the DNA template as an irreversible complex, and chain termination following incorporation into the viral DNA.

The bioavailability of oral acyclovir is 15-20% and is unaffected by food. The half-life is about 3 hours in patients with anuria. Acyclovir is readily cleared by hemodialysis but not peritoneal dialysis. Acyclovir diffuses into most tissues and body fluids to produce concentrations that are 50-100% of those in serum. Cerebrospinal fluid concentrations are 50% of serum values. Oral acyclovir is used in primary genital herpes. Intravenous acyclovir is the treatment of choice for herpes simplex encephalitis HSV or VZV infections. In immunocompromised patients with zoster, intravenous acyclovir reduces the incidence of intravenous and visceral dissemination. Topical acyclovir is much less effective than oral therapy for primary HSV infection. Resistant to acyclovir can develop in HSV or VZV through alteration in either the viral thymidine kinase or the DNA polymerase. Infections that are clinically resistance to acyclovir have been reported in immunocompromised host. Adverse reactions include nausea, vomiting, and headache. Tremors, delirium, seizures are uncommon and may not occur if there is adequate hydration and avoidance of rapid infusion rates.

3.1.1 Agents used to Treat Cytomegalovirus (CMV) Infections

Ganciclovir is an acyclic guanosine commonly used to treat cytomegalovirus (CMV) infections. Ganciclovir has in vitro activity against CMV, HSV, VZV, EBV, and HHV-8. Its activity against CMV is up to 100 times greater than that of acyclovir. Ganciclovir may be administered intravenously, orally or via intraocular implant. The half-life is 2-4 hours with normal renal function. Ganciclovir is readily cleared by haemodialysis. The bioavailability of oral ganciclovir is poor (6-9% when taken with food). Intravenous ganciclovir has been shown to delay progression of CMV retinitis in patients with AIDS when compared with no treatment. Dual

therapy with foscarmet and ganciclovir has been shown to be more effective in delaying progression of retinitis than either drug administered alone, though side effects are compounded. Intravenous ganciclovir is also used to treat CMV colitis and esophagitis. Oral ganciclovir is indicated for prevention of end-organ CMV disease in AIDS patients and as maintenance therapy of CMV retinitis following induction. Sporadic cases of ganciclovir resistant CMV infection have been reported since the introduction of ganciclovir in the late 1980s. Clinical manifestation may include progressive disease or prolonged viremia. Until recently majority of the resistant cases were in patients with AIDS receiving prolonged therapy with ganciclovir. The most common side effects, more common with intravenous administration than oral, is myelosuppression particularly neutropenia.

3.2 Antiretroviral Agents

A large and increasing number of anti- retroviral agents are currently available for treatment of HIV- infected patients

Examples are Abacavir - 300mg bid, Delavidine 400mg tid, Lamivudine 150mg or 300mg qid depending on weight, nevirapine 200mg bid. When to initiate therapy is controversial but it is important that monotherapy with any one agent should be avoided because of the need for maximal potency to durably inhibit virus replication and to avoid premature development of resistance. A combination of agents (Highly Active Anti-Retroviral Therapy HAART) is usually effective in reducing plasma HIV RNA and in gradually increasing CD4 cell counts particularly in antiretroviral - naive patients.

Also important in selection of agents is optimization of adherence, tolerability and convenience. Many patients will ultimately experience at least one treatment failure, close monitoring of viral load and CD4 cell counts is critical to trigger appropriate changes in therapy. The correct use of drug resistance testing is very important in selecting an alternative regimen for a patient who is not responding to therapy.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs): The NRTIs act by competitive inhibition of HIV-I reverse transcriptase and can also be incorporated into the growing viral DNA chain to cause termination. Each requires intracytoplasmic activation as a result of phosphorylation by cellular enzymes to the triphosphate form, most have activity against HIV-2 and HIV-I. The adverse reactions of NRTIs are lactic acidemia, severe hepatomegaly with steatosis. Other NRTIS are Zidovudine, Didanosine, Lamivudine, Zalcitabine, Stavudine, Abacavir. Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIS) are Nevirapie, Delarvirdine, Efavirenz.

3.3 Importance of Pharmacokinetics in the Treatment of HIV Infected Individuals

Patients who have HIV are frequently taking multiple medication, including combinations of antiretroviral agents, prophylaxis or treatment for opportunistic infections, and opioid pain medications or methadone for maintenance therapy, because of this, the physician caring for an HIV infected patient must have knowledge of clinical efficacy, adverse reactions, emergence of resistance and basic pharmacokinetics. For example an HIV infected patient receiving Ganciclovir for treatment of cytomegalovirus retinitis may be unable to tolerate concomitant therapies with the potential for additive myelosuppression, including zidovudine, ribavirin or the interferons.

Prescription of Abacavir may be complicated by the fact that alcohol decreases the AUC of Abacavir by 14%, the patient should be made aware of this potentially harmful interaction.

SELF ASSESSMENT EXERCISE

Name 4 Antiretroviral Agents used in the treatment of HIV/AIDS and their doses

	Antiviral agent	Doses
a.	.....	.....
b.	.....	.....
c.	.....	.....
d.	.....	

4.0 CONCLUSION

Viruses are obligate intracellular parasites whose replication depends primarily on synthetic processes of the host cell. Potent inhibition of viral replication may be of clinical benefit in chronic illness such as HIV infection or viral hepatitis.

5.0 SUMMARY

A combination of agents (highly active antiretroviral therapy HAART) is usually effective in reducing plasma HIV RNA levels and in

gradually increasing CD4 cell counts, particularly in antiretroviral naive patients. Antiretroviral agents include Nucleoside reverse transcriptase inhibitors (NRTLS), Nucleotide Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors and others

ANSWER TO SELF ASSESSMENT EXERCISE

	Antiviral Agents	Doses
a.	Abacavir	300mg bid
b.	Delavidine	400mg tid
c.	Lamivudine	150mg / 300mg qid
d.	Nevirapine	200mg bid

6.0 TUTOR-MARKED ASSIGNMENT

Discuss the antiretroviral agents.

7.0 REFERENCES/FURTHER READINGS

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UNIT 5 ANTIFUNGAL AGENTS

CONTENTS

1.0 INTRODUCTION

The increased use of broad spectrum antimicrobials, advances in surgery, cancer treatment and HIV epidemic have increased human fungal infections. Pharmacotherapy of fungal disease has been revolutionized by the introduction of the relatively non-toxic oral azole drugs and the echinocandins. Combination therapy is being reconsidered the new formulations of old agents are becoming available the appearance of *ozone* resistant organisms, as well as the rise in the number of the patient at risk of mycotic infections has created new challenges. Antifungal drugs are classified into systematic drugs (oral or parenteral) for systematic infections oral drugs for mucocutaneous infections and topical drugs for mucocutaneous infections.

2.0 OBJECTIVES

At the end of the unit the learner will:
- understand the three categories of antifungal drugs
- know the pharmacokinetics of antifungal agents
- know the specific uses of antifungal agents.

3.0 MAIN CONTENT

3.1 Amphotericin B

Amphotericin A and B are antifungal antibiotics produced by *Streptomyces nodosus. Amphotericin* A is not used clinically. Amphotericin B is an amphoteric polyene macrolide it is nearly insoluble in water. Several new formulations have been developed in which amphotericin B is packaged in a lipid-associated delivery system.

Pharmacokinetics: Amphotericin B is poorly absorbed from the gastrointestinal tract. Oral amphotericin B is thus effective only on fungi within the lumen of the tract and cannot be used for treatment of systematic disease. The drug is more than 90% bound by serum proteins, it is mostly metabolized and some amphotericin B excreted slowly in the urine over a period of several days. The serum half-life is approximately 15 days. The drug is widely distributed in most tissues but only 2-3% of the blood level is reached in cerebrospinal fluid, thus occasionally necessitating intrathecal therapy for certain type of fungal meningitis. Amphotericin B is selective in its fungicidal effect because it exploits the difference in lipid composition of fungal and mammalian cell membranes. Amphotericin B combines avidly with lipids (ergosterol) along the double bound rich side of its structure and associate with water molecules along the hydroxyl- rich side.

This amphipathic characteristic facilitates pore formation by multiple amphotericin molecules, with the lipophilic portions around the outside of the pore and the hydrophilic region lining the inside. The pore allows the leakage of intracellular and macromolecules eventually leading to cell death. Some binding to human membrane sterols does occur, probably accounting for the drugs' prominent toxicity. Adverse reactions of amphotericin B include fever, chills, muscle spasms, vomiting, headache, renal damage.

Amphotericin B has activity against yeasts including *Candida albicans* and *Cryptococcus neoformans, Histoplasma capsulatum.* It is the drug of choice in nearly all life threatening mycotic infections.

3.2 Ketoconazole

It is the first oral azole introduced into clinical use. It is distinguished from triazoles by its greater propensity to inhibit mammalian cytochrome P450 enzymes, i.e. it is less selective for fungal P450 than are the newer azoles. Ketoconazole (Nizoral) is available as a cream for topical treatment of dermatophytosis and candidiasis and as a shampoo for the treatment of seborrheic dermatitis.

3.3 Nystatin

It is a polyene macrolide much like amphotericin B it is too toxic for parental administration and it is only used topically. It is currently available in creams, ointments, suppositories, and other forms for application to skin and mucous membranes. Nystatin is not absorbed to a significant degree from the skin, mucous membranes, or the gastrointestinal tract. As a result, it has little

toxicity, though oral use is often limited by the unpleasant taste. It is most commonly used for suppression of local candida infections, oropharyngeal thrush, vaginal candidiasis, and inter-inguinal candida infections.

3.4 Griseofulvin

It is an insoluble fungistatic drug derived from a species of penicillium. It is used in the systematic treatment of dermatophytosis. It is administered in a microcrystalline form at a dosage of 1g/d. Absorption is improved when it is given with fatty foods. Griseofulvin is deposited in newly forming skin where it binds to keratin, protecting the skin from new infections. Because of this, it must be administered for 2-6 weeks for skin and hair infections to allow the replacement of infected keratin by the existing structures.

3.5 Fluconazole

It is highly water soluble and has good cerebrospinal fluid penetration. Unlike ketoconazole and itraconazole, its oral bioavailability is high. Drug interactions are also common because fluconazole has the least effect of all the azoles on hepatic microsomal enzymes. Because of few hepatic enzymes interactions and better gastrointestinal tolerance, fluconazole has the widest therapeutic index of azoles permitting more aggressive dosing in a variety of fungal infections. The drug is available in oral and intravenous formulation and is used at a dosage of 100-800mg/d. Fluconazole is the azole of choice in the treatment and secondary prophylaxis of cryptococcal meningitis. Intravenous fluconazole has been shown to be equivalent to amphotericin B in treatment of candidemia in patient with normal white blood cell counts. Fluconazole is most commonly used for the treatment of mucocutaneous candidiasis. Prophylactic use of fluconazole has been demonstrated to reduce fungal disease in bone marrow transplant recipients and AIDS patients, but the emergence of fluconazole-resistant fungi has raised concerns about the indication.

SELF ASSESSMENT EXERCISE

1. Name the 3 categories of antifungal drugs and examples.

   a.....
   b .....
   c. .....

2. State the uses of fluconazole

   a ……
   b .....
   c. .....
   d. .....

4.0 CONCLUSION

Fungi infections are stubborn infections which sometimes take more than six weeks to treat. Some of the antifungal agents now available are Amphotericin B, Ketoconazole, Nystatin and Griseofulvin.

5.0 SUMMARY

Antifungal drugs could be systemic drugs (oral or parenteral) for systemic infections, oral drugs for mucocutaneous infections and topical drugs for mucocutaneous infections.

ANSWER TO SELF ASSESSMENT EXERCISE

1. a. Systemic drugs (oral or parenteral) for systemic Infections.
   b. Oral drug for mucocutaneous infections
   c. Topical drugs for mucocutaneous infections.

2. Uses of fluconazole

   a. Secondary prophylaxis of cryptococcal meningitis.
   b. Candidemia

c. Mucocutaneous candidiasis

To reduce fungal disease in AIDs patients who receive bone marrow transplant.

6.0 TUTOR-MARKED ASSIGNMENT

Fluconazole is an antifungal agent, discuss.

7.0 REFERENCES/FURTHER READINGS

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UNIT 6 CHEMOTHERAPY OF CANCER 106

CONTENTS

1.0 INTRODUCTION

Cancer is a disease of cells characterized by a shift in the control mechanisms that govern cell proliferation and differentiation. Cells that have undergone neoplastic transformation usually express cell surface antigens that may be of normal fetal type. They may show other signs of apparent immaturity, and may exhibit qualitative or quantitative chromosomal abnormalities, including various translocations and the appearance of amplified gene sequences. Such cells proliferate excessively and form local tumors that can compress or invade adjacent normal structures. A small subpopulation of cells within the tumor can be described as tumor stem cells. They retain the ability to undergo repeated cycles of proliferation as well as to migrate to distant sites in the body to colonize various organs in the process called metastasis. The incidence, geographic distribution, and behaviour of specific types of cancer are related to multiple factors, like sex, age, race, genetic predisposition and exposure to environmental carcinogens. Of these factors, environmental exposure is probably most important. Chemical carcinogens (particularly those in tobacco smoke) as well as azodyes, aflatoxins, asbestos, and benzene have been clearly implicated in cancer induction in humans and animals. Identification of potential carcinogens in the environment has been greatly simplified by the use of Ames test for mutagenic agents. Ninety percent (90%) of carcinogens can be shown to be mutagenic, with this assay. Cancer is the second most common cause of death in the USA, the first is heart disease. It causes over 500,000 fatalities annually. Local modalities (surgery or radiation therapy) are effective when the tumor has not metastasized by the time of treatment. Early micrometastasis is a characteristic feature of the neoplasm indicating that a systemic approach such as chemotherapy is required (often along with surgery or radiation) for effective cancer management.

At present about 50% of patients with cancer can be cured, with chemotherapy contributing to cure in 10-15% of patients

2.0 OBJECTIVES

At the end of the unit the learner will:

- know the causes of cancer
- understand the types of cancer.

3.0 MAIN CONTENT

3.1 Polyfunctional Alkylating Agents

The major clinically useful alkylating agents have a structure containing a bis (chloroethyl) amines. Among the bis (chloroethyl) amines, cyclophosphamide, mechloroethamine, melphalan, and chlorambucil are the most useful. Ifosfamide is closely related to cyclophosphamide but has a different spectrum of activity and toxicity. Thiotepa and busulfan are used specially for ovarian cancer, and chronic myeloid leukemia. The major nitrosoureas are carmustine (BCNU), lomustine, (CCNU), and semustine (methyl-CCNU). The alkylating agents exert cytotoxic effects via transfer of their alkyl groups to various cellular constituents. Alkylations of DNA within the nucleus probably represent the major interactions leading to cell death.

3.2 Nitrosoureas

These drugs appear to be non-cross-reactive with other alkylating agents; all require biotransformation, which occurs by non-enzymatic decomposition, to metabolites with both alkylating and carbamoylating activities. The nitrosoureas are highly lipid-soluble and cross the blood - brain barrier, making them useful in the treatment of brain tumors. The nitrosoureas appear to function by cross-linking through alkylation of DNA. The drugs may be more effective against plateau phase cells than exponentially growing cells, though within a cycling cell population these agents appear to slow cell progression through the DNA synthetic phase. After oral administration of lomustine, peak plasma levels of metabolites appear within 1-4 hours, central nervous system concentration reaches 30 - 40% of the activity present in the plasma. The initial plasma half-life is in the range of hours, a second half-life is in the range of 1-2 days. Urinary excretion appears to be the major route of elimination from the body. One naturally occurring sugar-containing nitrosourea, streptozotocin, is an interesting one because it has minimal bone marrow toxicity. This agent has activity in the treatment of insulin-secreting islet cell carcinoma of the pancreas.

3.3 Antimetabolites

Biochemical properties unique to all cancer cells are yet to be discovered. Neoplastic cells have a number of quantitative differences in metabolism from normal cells that render them more susceptible to a number of anti-metabolites or structural analogs. Many of these agents have been rationally designed and synthesized based on knowledge of cellular processes, and a few have been discovered as antibiotics. The pathways that have thus proved to be most vulnerable to antimetabolites have been those relating to nucleotide and nucleic acid synthesis. In a number of instances, when an enzyme is known to have a major effect on pathways leading to cell replication, inhibitors of the reaction it catalyzes have proved to be useful anticancer drugs.

Example of antimetabolites is methotrexate. Methotrexate (MTX) is a folic acid antagonist that binds to the active catalytic site of dihydrofolate reductase (DHFR), interfering with the synthesis of the reduced form that accepts one-carbon units. Lack of this cofactor interrupts the synthesis of thymidylate, purine serine and methionine, thereby interfering with the formation of DNA, RNA, and proteins. Methotrexate dosage is 2.5 - 5mg/day orally (Rheumatrex), 10mg intrathecally (folex) once or twice weekly. Methotrexate is also used in the treatment of rheumatoid arthritis and psoriasis. Its delayed toxicities are mucositis, diarrhoea, bone marrow depression with leucopenia and thrombocytopenia. Some of the other antimetabolites are cladribine, cytarabine, fluorouracil and thioguanine.

3.4 Plant alkaloids

Vinblastine is an alkaloid derived from *Vinca rosea,* the periwinkle plant. Its mechanism of action involves depolymerization of microtubules, which are an important part of the cytoskeleton and the mitotic spindle. The drug binds specially to the microtubule protein tubulin in dimeric form; the drug-tubulin complex adds to the forming end of the microtubules to terminate assembly, and depolymerization of the microtubules occurs. This results in dissolution of the mitotic spindle, and interference with chromosome segregation. Toxicity includes nausea, vomiting, bone marrow suppression and alopecia.

Vincristine: Vincristine is an alkaloid derivative of *Vinca rosea* and is closely related in structure to vinblastine. Its mechanism of action is identical to that of vinblastine in that it functions as a mitotic spindle poison leading to arrest of cells in the metaphase of the cell cycle. Despite the similarities to vinblastine, vincristine has a strikingly different spectrum of clinical activity and qualitatively different toxicities. Vincristine has been effectively combined with prednisone for remission induction in acute lymphoblastic leukemia in children. It is also active in various malignancies such as Hodgkin's and non-Hodgkin lymphoma and multiple myeloma and in several paediatric tumors including rhabdomyosarcoma, neuroblastoma, Ewing's sarcoma, and Wilm's tumor. The main dose-limiting toxicity is neurotoxicity, usually expressed as a peripheral sensory neuropathy, autonomic nervous system dysfunction, with orthostatic hypotension, sphincter problems and paralytic ileus, cranial nerve palsies, ataxia, seizures, and coma have been observed. It causes myelosuppression which is less significant than with vinblastine. Other potential side effects that can develop is the syndrome of inappropriate secretion of antidiuretic hormone.

Other plant alkaloids are vinorelbin, epipodophylotoxins, camptothecins and taxanes.

SELF ASSESSMENT EXERCISE

Name the 4 groups of anticancer drugs discussed and give examples.

a. .....
b. .....
c. .....
d. .....

4.0 CONCLUSION

Cancer chemotherapy can be curative in certain disseminated neoplasms that have undergone gross or microscopic spread e.g testicular cancer, non-Hodgkin's disease. In some cases e.g. breast cancer, esophageal cancer, rectal cancer and osteogenic sarcoma, chemotherapy is combined with initial surgery to increase the cure rate.

5.0 SUMMARY

Drugs used in the treatment of cancer are polyfunctional alkylating agents, nitrosoureas, Antimetabolites and Plant alkaloids.

ANSWER TO SELF ASSESSMENT EXERCISE

- Polyfunctional Agent e.g. Nitrosoureas
- Nitrosoureas e.g. streptozotocin
- Antimetabolites e.g. Methotrexate
- Plant alkaloids e.g. vinblastine, vincristine

6.0 TUTOR-MARKED ASSIGNMENT

Vinblastine is a plant alkaloid used in treating cancer. Discuss its mechanism of action.

7.0 REFERENCES/FURTHER READINGS

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MODULE 5 PARASITIC INFECTIONS

Unit 1 Chemotherapy of Malaria
Unit 2 Chemotherapy Helminthic Infections

UNIT 1 CHEMOTHERAPY OF MALARIA

CONTENTS

1.0 INTRODUCTION

Malaria is the most wide spread of all tropical diseases. It is endemic in one hundred and two (102) countries. More than two hundred million people in the world have acute malaria yearly. Most of these are in Africa. The name malaria is obtained from the Italian word “mal Aria” meaning bad air. The disease is known as paludism from the latin word “palus”, meaning marsh. Both names reflect the early opinion that the disease was spread by miasma or mist arising in marshes. Malaria is a protozoan disease, the causative organism being the plasmodium - namely *Plasmodium falciparum, P. ovale, P. malariae* and *P vivax.*

2.0 OBJECTIVES

At the end of the unit the learner will understand:
- the epidemiology of malaria
- the pathology and clinical features of malaria
- the chemotherapy and chemoprophylaxis used in malaria treatment.

3.0 MAIN CONTENT

3.1 Transmission

Malaria is transmitted from man to man by anopheles mosquitoes which are varied in species. Some are very efficient; others not so efficient and still others are not capable of transmission. Malaria can be transmitted in other ways either by design or by accident, by inoculation of blood from an infected person to a healthy person. Malaria transmitted by inoculation of blood is easily cured and relapses don’t occur but P. *falciparum* infections transmitted in this way can be fatal. The chief operations by such transmissions of infections are (1) deliberate infection in neurosyphilis for curative purposes. *P vivax* is commonly used but other species can be used too. (2) Unintentional infection through transfusion of blood which, unknown to the physician contains malaria parasite. P vivax has been transmitted this way in temperate climate from donors infected three years before while *P. ovale* from donors affected four years earlier. The *P falciparum* is present in blood from donors who are exposed 20 months to 3 years earlier. The number of instances of transmission of malaria is higher in countries where the system of blood donation is commercialized. Dried plasma prepared from malaria blood is safe. The microscopic examination of blood is not very helpful in the detection of infected donors, but in special circumstances the immunofluorescent test (IFA) has proved useful.

3.2 Epidemiology of malaria

The existence of malaria is determined by the presence of anopheles vector, breeding in nature where human carriers of the sexual forms of the parasites are available to these mosquitoes. There are only few areas in the world where anopheles vectors are present in the absence of malaria. As a result of control and eradication procedures many former malarious areas are now clear because the anopheline population has been reduced or eliminated. In areas where malaria persists the epidemiology of the disease is resultant of various factors which could be classified as:

- Factors relating to man,
- Factors relating to the parasite,
- Factors relating to the anopheles.

These complex biological factors obviously overlap and interact to provide various degrees of stability or instability in the prevalence of malaria. They are particularly evident in the epidemiology of *P. falciparum* malaria.

3.3 Pathology of Malaria

The pathology of malaria is essentially the pathology of *P. falciparum* infection. Various schools of thought do not think that malarial infections interfere sufficiently with haemoglobin, either by destruction of erythrocytes or by conversion to haemozoin, to affect the oxygen carrying function of the blood, nor is the oxygenation function of the lungs sufficiently impaired in malaria. The erythrocyte become sticky with a coat of fibrin and it has long been taught that this causes agglutination and obstruction in smaller vessels. Neither clots nor emboli are involved in this process. Hypovolemia may be a factor. Certain chemical changes occur when the blood is infected with malaria parasite. Plasma protein is reduced, especially albumin, though globulin is increased. These changes are not due to fever alone but related to offset in liver function. Glucose is essential for the respiration of plasmodia and rise of blood sugar occurs both in *P falciparum* and *P. vivax* infections, possibly connected with a change in adrenal function. The Erythrocyte sedimentation rate (ESR) is raised when one has malaria but will restore to normal after treatment.

3.4 Clinical Features of Malaria

P. falciparum malaria (malignant tertian) this is the fatal form of malaria which can kill a non-immune person within a week or two of a primary attack, unless appropriate treatment is given on time. With *P. falciparum* symptoms are generally relatively slight in the early stages. It is characteristic of tertian fever accompanied by clinical syndrome of three stages - cold (lasting and piles on bed clothes), Hot (lasting three to four hours when the patient's temperature is high), the skin dry and he throws off the bed clothes soaked in sweat and his temperature falls rapidly to relieve the patient but he get exhausted. These three stages occur on alternate days in accordance with the cycle of the parasite. The patient feels very miserable, there are instances where a double infection occurs (with some parasite maturing on day 1, 3, etc.) which shows daily rise of temperature but this is an uncommon situation. It is important to mention here that *P. falciparum* malaria is very variable, mimicking many other condition and taking several forms which may be misleading. Other forms of *P. falciparum* malaria are cerebral malaria: - A form of pernicious attack with hyperpyrexia to 41.6°C or more at 5% or more of erythrocytes infected. Patient may be delirious or comatose with general muscle twitching, disorientation and incontinence. There may be epileptic attack. Algid malaria: The surface of the body is cold and the temperature falls rapidly to below normal. Blood pressure also falls alarmingly and coma sets in followed by death within a few hours.

3.5 Drug Treatment

Chemotherapy:-The strategy currently recommended by WHO for the control of malaria in Africa is the reduction of morbidity and mortality from the disease through chemotherapy. Since cornerstone of malaria chemotherapy until recently when there is a lot of resistance to chloroquine and chloroquine is giving way to artemisinin combined derivatives. Chemotherapy of malaria can be divided into Actual drug treatment and chemoprophylaxis

Drug treatment: Quinine dihydrochloride.
Quinine dihydrochloride is used against sexual blood forms, but has no action on matured gametocytes of *P. falciparum.* It is effective against gametocytes of *P. vivax* and *P. malaria.* It is particularly useful in cerebral or other dangerous forms where rapid clearance of the blood is needed. Its action in cerebral malaria like chloroquine and the corticosteroid is anti-inflammatory, reversing the leakage of protein and water from small vessel and restoring the circulation. Adult dose is 650mg three times daily for 10-14 days.

Quinine Hydrochloride can be given in emergencies by slow intravenous injection of 500mg to 650mg in 15-20ml saline or distilled water sterilized by heat.

4-Aminoquinolines: Chloroquine is important in this group. It has a strong action on erythrocytic asexual parasite of all species and is the drug of choice for acute attack. It becomes highly concentrated in the liver and in parasitized erythrocytes within a few minutes of administration. It has no action on matured gametocytes of *P. falciparum* but does act against those of *P. vivax, P. ovale* and *P. malariae.* Chloroquine phosphate (Aralen, evlovlor, resoclin etc.) is given by mouth in a first (immediate) dose of 600mg base (1000mg salt): or chloroquine 600mg base (500mg salt). This first dose is followed in six hours by 300mg 2-4 days bringing the total dose to 1500-2400mg base. The strain of *P. falciparum* resistant to chloroquine is increasingly being reported from South East Asia, America and Africa and resistance to chloroquine is usually accompanied by resistance to other 4-aminoquinolines such as amodiaquine. This is why artemisinin derivatives are often used as anti-malaria these days. Amodiaquine hydrochloride (e.g. camoquine) should be given in a dose of 600mg base (783mg salt). Immediately, followed by 400-600mg base daily for two days, to a total dose of 1400-2400mg base. Agranulocytosis coinciding with treatment was reported in New Guinea.

8-Aminoquinolines: - The earliest drug of this series was pamaquine given in doses of 10-20mg, but this has been superseded by primaquine phosphate given at a dose of 13mg (7.5mg base) twice daily for 10 to 14days. They are potentially toxic, especially in persons with glucose 6- phosphate dehydrogenase deficiency, in whom they may precipitate acute haemolysis

Acridine: The most notable acridine compound in relation to malaria is Mepacrine (e.g. quinacrine) it is seldom used at present but was a powerful substitute for quinine in the war of 1939 - 1945 (Second World War).It is highly concentrated in liver cells and leucocytes. It has little action on strains of *P. falciparum* resistant to chloroquine and it has no action on gametocytes.

Sulphonamides: sulphodiazine has some antimalarial action but it is not a rapid schizontocides. A study reported by Mcgregor showed that in pyrimethamine-resistant *P. falciparum* infection in an African child, 12.5mg with a 1g sulphadiazine, repeated after 24 hours eliminated the parasites from the blood, thus suggesting a potentiating effect which has been studied more extensively in recent times. The long acting sulphonamide, sulphomelhaxine (sulphadoxine) can clear asexual *P. falciparum* from the blood and is useful where chloroquine resistance is formed. It gives high blood concentration and is excreted very slowly. A combination of pyrimethamine, 25mg, with sulphadoxine 500mg known as fansidar, has proved of great value in the treatment of chloroquine-resistant *P. falciparum.* However resistant to sulphonamides have been reported in strains of *P. falciparum*

Artemisia annua: Artemisinin (Qingahosu) is a sesquiterpene lactone endoperoxide, the active component of an herbal medicine that has been used as an antipyretic in china for over 2000 years. Artemisinin is insoluble and can only be used orally. Analogs have been synthesized to increase solubility and improve antimalaria efficacy. The most important of these analogs are artesunate (water-soluble; useful for oral, intravenous, intramuscular, and rectal administration), two other important analogs under study are artemether and artelinic acid. Artemisinin and its analogs are rapidly absorbed with peak plasma levels occurring in 1-2 hours and half-lives of 1-3hours after oral administration. The compounds are rapidly metabolized to the active metabolite dihydro artemisinin. Drug levels appear to decrease after a number of days of therapy. Artemether and artesunate are available in Nigeria. Artesunate is widely available - although quite expensive for the treatment of uncomplicated and severe falciparum malaria. The most commonly reported adverse effects have been nausea, vomiting, and diarrhoea. Artemisinins should be avoided in pregnancy if possible because teratogenicity has been seen in animal studies.

Chemoprophylaxis: The main drug for continuous administration is proguanil (paludrine). It has a slow action against asexual blood forms of all malaria parasites and some action on tissue schizonts of *P. falciparum.* The adult dose is 100-200mg daily starting the day before entering into a malarious area. The next commonly used drug is pyrimethamine (e.g daraprim) which mainly acts on gametocytes preventing their development in mosquitoes. It acts slowly on asexual malaria parasite in the blood. Daily doses may be toxic resulting in leucopenia and the regular fever. Proguanil - Dose 100 - 200mg daily, pyrimethamine 25mg weekly, chloroquine 300mg weekly and
Amodiaqine (base) is 400mg or more weekly.

SELF ASSESSMENT EXERCISE

Mention the drugs used in the treatment of malaria and their doses.

a. .....
b. .....
c. .....
d. .....
e. .....
f. .....

4.0 CONCLUSION

Total eradication of malaria has for several years been the aim of WHO. The use of insecticide treated bed net, clearing the environment of bushes, careful use of drugs for prophylaxes and deal of malarial infection from the society.

5.0 SUMMARY

Malaria is a protozoan disease, the causative organism being the plasmodium i.e. *Plasmodium falciparum, P ovale, P. malaria and P vivax.* Drugs used in the treatment of malaria are 4-Aminoquinolines (chloroquine), 8 - aminoquinolines (primaquine), quinine hydrochloride, acridines, sulphonamide, artemisininin derivatives (Artesunate).

ANSWER TO SELF ASSESSMENT EXERCISE

Drugs used in the treatment of malaria

a. 4-aminoquinolines Dose 1000mg starter
b. 8-aminoquinolines Dose 13mg twice daily for 10 - 14 days
c. Quinine hydrochloride Dose 650mg three times daily for 10 - 14 days
d. Acridines dose- no longer in use
e. Sulphonamide dose sulphadoxine 500mg Pyrimethamine 25mg
f. Artemisinin derivative Dose combination drug.

6.0 TUTOR-MARKED ASSIGNMENT

Discuss the epidemiology of malaria and the use of artemis in its treatment.

7.0 REFERENCES/FURTHER READINGS

Bertram G. Katzung and Todd W. Vanderah. *Basic and Clinical Pharmacology,* 15th Edition, 2020.

https://www.who.int/news-room/fact-sheets/detail/malaria

UNIT 2 CHEMOTHERAPY OF HELMINTHIC INFECTIONS

CONTENTS

1.0 INTRODUCTION

Parasitic infections are a major worldwide health problem particularly in the developing world where these conditions have caused a substantial economic burden. The global prevalence of human parasitic infections already exceeds 50% and is increasing. Factors responsible for this high incidence are overcrowding, poor sanitation and health education, inadequate control of parasitic vectors and reservoir of infections, increased world travel. Helminthic infection chemotherapy remains the single most effective, efficient and inexpensive method to control most parasitic infections after taking public health measures appropriate for the particular infections i.e environment and host population. Worm infection is a disease of children in developing countries.

2.0 OBJECTIVES

At the end of the unit the learner will:

- understand what helminthic infections are.
- know the various drugs used in the treatment of helminthic infection.

3.0 MAIN CONTENT

3.1 Albendazole

It is a broad-spectrum oral anthelminthic. It is used for the treatment of hydatid disease and cysticercosis. It is used for the treatment of pinworm and hook worm infections, ascariasis, trichuriasis and strongyloidiasis. Albendazole is a benzimidazole carbamate. After oral administration, it is erratically absorbed (increased with a fatty meal) and then rapidly undergoes first-pass metabolism in the liver to active metabolite, albendazole sulfoxide. It reaches variable maximum plasma concentrations about 3 hours after a 400mg oral dose, and its plasma half-life is 8 to-12 hours. The sulfoxide is mostly protein-bound, distributes well to tissues, and enters bile, cerebrospinal fluid, and hydaticysts. Albendazole metabolites are excreted in the urine.

Mechanism of Action: benzimidazoles act against nematodes by inhibiting microtubule synthesis. Albendazole also has larvicidal effects in hydatid disease, cysticercosis, ascariasis, and hook worm infections, and ovalcidal effects in ascariasis, ancylomiasis, and trichuriasis.

Albendazole is administered on an empty stomach when used against intraluminal parasites but with a fatty meal when used against tissue parasites. Dose: 400mg orally (repeated for 2-3 days for heavy ascaris infections and in 2 weeks for pin worm infections). These treatments achieve high cure rates for these round worm infections and marked reduction in egg counts in those not cured.

3.2 Diethyl Carbamazine Citrate (Banocide)

Diethylcarbamazine is a drug of choice in the treatment of filariasis, loiasis, and topical neosinophilia. It has been replaced by ivermectin for the treatment of onchocerciasis. It is a synthetic piperazine derivative marketed as a citrate salt. It is rapidly absorbed from the gastro intestinal tract, after a 0.5mg/kg dose, peak plasma levels are reached within 12hours. The plasma half-life is 2-3hours in the presence of acidic urine but about 10 hours if the urine is alkaline. The drug rapidly equilibrates with all tissues except fat. It is excreted, principally in the urine, as unchanged drug and the N-oxide metabolite. Dosage may have to be reduced in patient with persistent urinary alkalosis or renal impairment.

Mechanism Action: Diethyl carbamazine immobilizes microfilaria and alters their surface structure displacing them from tissues

and making them more susceptible to destruction by host defense mechanism. The mode of action against adult worms is unknown. The drug should be taken after meals.

Diethylcarbamazine is the drug of choice for treating *Wuchereria bancrofti, Brugia malayi, Brugia timori* and *Loaloa.* These infections are treated for 2 or 3 weeks, with initial low doses to reduce the incidence of allergic reaction to dying microfilaria. The regimen is 50mg on day 1, three 50mg doses on days 2, three 100mg doses on days 3 and then three 100mg doses to complete the 2-3week course. Anti-histamines may be given for the first few days of therapy to limit allergic reactions and corticosteroids should be started and doses of diethylcarbamazine lowered or interrupted, if severe reactions occur. Adverse reactions which are generally mild and transient include headache, malaise, anorexia, weakness, nausea vomiting and dizziness.

3.3 Ivermectin

It is the drug of choice in strongyloidiasis and onchocerciasis. It is also an alternative drug for a number of other helminthic infections. Ivermectin is a semi-synthetic macrocyclic lactone, a mixture of avermectin B_{19} and B_{16}. It is derived from the soil actinomycete, *Streptomyces avermitilis.* It is used only orally in humans. The drug is rapidly absorbed, reaching maximum plasma concentration 4 hours after a 12mg dose. The drug has a wide tissue distribution and a volume of distribution of about 50L, its half-life is about 16 hours. Excretion of the drug and its metabolites is almost exclusively in the feces.

Mechanism of Action: Ivermectin appears to paralyze nematodes and arthropods by intensifying GABA-mediated transmission of signals in peripheral nerves in onchocerciasis, ivermectin is microfilaricidal. It does not effectively kill adult worms but blocks the release of microfilaria for some months after therapy. After a single standard dose, microfilaria in the skin diminishes rapidly within 2-3 days, remain low for months and then gradually increase. Dose for onchocerciasis is a single dose of 150µg/kg with water on an empty stomach.

Ivermectin plays a key role in onchocerciasis control. Adverse reactions that can occur after taking ivermectin are fever, headache, dizziness, somnolence, weakness, rash, increased pruritus, diarrhoea, joint and muscle pains, hypotension, tachycardia, lymphadenitis, lymphangitis and peripheral edema.

3.4 Niclosamide

Niclosamide is a second line drug for the treatment of most tapeworm infections. It is a salicylamide derivative. It appears to be minimally absorbed from the gastro intestinal tract - neither the drug nor its metabolites have been recovered from the blood or urine.
Adult worms are rapidly killed, presumably due to inhibition of oxidative phosphorylation or stimulation of ATPase activity. The adult dose of niclosamide is 2g once, given in the morning on an empty stomach. The tablets must be chewed thoroughly and are then swallowed with water. Niclosamide is effective in treating *T. saginata* (Beef tapeworm), *T. Solium* (Pork tapeworm) and *Diphyllobothrium latum* (fish tapeworm). Adverse reactions are nausea, vomiting, diarrhoea and abdominal discomfort. It is contraindicated in pregnancy.

3.5 Praziquantel

Praziquantel is effective in the treatment of schistosome infections of all species and most other trematode and cestode infections including cysticercosis. The drug's safety and effectiveness as a single oral dose have also made it useful in mass treatment of several infections. Praziquantel is a synthetic isoquinoline-pyrazine derivative. It is rapidly absorbed with a bioavailability of about 80% after oral administration. Peak serum concentrations are reached 1l-3hours after a therapeutic dose. Cerebrospinal fluid concentrations of praziquantel reach 14-20% of the drugs plasma concentration. Praziquantel appears to increase the permeability of trematode and cestode cell membranes to calcium resulting in paralysis, dislodgement and death. In schistsome infections of experimental animals, praziquantel is effective against adult worms and immature stages and it has a prophylactic effect against cercarial infection. Praziquantel tablets are taken with liquid after a meal. They should be swallowed without chewing because their bitter taste can induce retching and vomiting. Praziquantel is used treat schistosomiasis. The dosage is 20mg/kg for *S. mansoni* and *S. haematobium.* Praziquantel 5-10mg/kg can be used to cure *T. saginata* and *T. solium.*

3.6 Pyrantel Pamoate

Pyrantel pamoate is a broad-spectrum anthelminthic highly effective for the treatment of pinworm, ascaris, and *Trichostrongylus orientalis* infections. It is moderately effective against both species of hookworm. It is not effective in trichuriasis or strongyloidiasis. Oxantey pamoate, an analogue of pyrantel, has been successfully used in the treatment of trichuriasis, the two drugs have been combined for their broad spectrum anthelminthic activity. It is a tetrahydro pyrimidine derivative. It is poorly absorbed from the gastro intestinal tract and active mainly against luminal organisms. Peak plasma levels are reached in 1-3hours.

Over half of the administered dose is recovered unchanged in the faeces. It is effective against mature and immature forms of susceptible helminthes within the intestinal tract but not against ova. The drug is a neuromuscular blocking agent that causes release of acetylcholine and inhibition of cholinesterase; this results in paralysis, which is followed by expulsion of worms. The standard dose is 1 mg (base)/kg (maximum 1g) given orally once with or without food. For pinworm the dose is repeated in 2 weeks, and cure rates greater than 95%. For ascariasis, a single dose yields cure rates of 85 - 100%. Adverse effects are infrequent, mild and transient. They include nausea, vomiting, diarrhoea, abdominal cramps, dizziness, drowsiness, headache, insomnia, rash, fever, and weakness.

3.7 Piperazine

Piperazine is an alternative for the treatment of ascariasis with cure rates over 90% when taken for 2 days. It is not recommended for other helminthic infections. It is available as the hexahydrate and as a variety of salts. It is readily absorbed, and maximum plasma levels are reached in 2-4hours. Most of the drug is excreted unchanged in the urine in 26hours, and excretion is complete within 24hours. Piperazine causes paralysis of ascaris by blocking acetylcholine at the myoneural junction: unable to maintain their position in the host, live worms are expelled by normal peristalsis. For ascariasis, the dosage of piperazine is 75mg/kg orally once daily for 2 days. For heavy infections treatment should be continued for 3-4 days or repeated after 1 week. Adverse effects are nausea, vomiting, diarrhoea, abdominal pain, dizziness, and headache.

SELF ASSESSMENT EXERCISE

List the anthelminthic drugs and give the side effects of pyrantel pamoate.

a. .....
b. .....
c. .....
d. .....
e. .....
f. .....
g. .....

Other side effects of pyrantel pamoate are.....

4.0 CONCLUSION

Worms are mainly diseases of children. It is common in areas where there is poor sanitation, and lack of health education. Children infested with worms are usually underdeveloped and it is a common disease in developing countries.

5.0 SUMMARY

Drugs used in the treatment of helminthic infections are Albendazole, Diethylcarbamazine citiate, ivermectin, Niclosamide, Praziquantel, Pyrantel pamoate and Piperazine. Others are Bithionol, Mebendazole, Metiifonate, and thiabendazole. Common side effects of anthelminthics are nausea, vomiting, diarrhoea and abdominal cramps.

ANSWER TO SELF ASSESSMENT EXERCISE

Anthelminthic drugs
Albendazole
Diethylcarbamazine citrate
Ivermectin
Niclosamide
Praziquantel
Pyrantel pamoate
Piperazine (Antepar)

Others are Bithionol, Mebendazole, Metrifonate, and thiabendazole. Side effects of Pyrantel pamoate are nausea, vomiting, diarrhoea and abdominal cramps, dizziness, drowsiness, headache, insomnia, rash, fever and weakness.

6.0 TUTOR-MARKED ASSIGNMENT

Discuss pyrantel pamoate in the treatment of worm infections.

7.0 REFERENCES/FURTHER READINGS

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MODULE 6 TRADITIONAL MEDICINE

Unit 1 Introduction into Traditional Medicine Practice
Unit 2 Medicinal Plants

UNIT 1 INTRODUCTION TO TRADITIONAL MEDICINE PRACTICE

CONTENTS

1.0 INTRODUCTION

Traditional medicine refers to health practices, approaches, knowledge and beliefs incorporating animal and mineral based medicines, spiritual therapies, manual techniques and exercises, singularly or in combination to treat, diagnose and prevent illness or maintain wellbeing.

Countries in Africa, Asia and Latin America use traditional medicine to help meet some primary health care needs. In Africa, up to 80% of the population uses traditional medicine healthcare. In industrialized countries, adaptations of traditional medicine are termed “complimentary or alternative”. Traditional medicine has maintained its popularity in all regions of the world.

2.0 OBJECTIVES

At the end of the unit the learner will:
- understand what traditional/alternative medicine is
- compare traditional medicine with orthodox medicine
- know the limitations of traditional medicine.

3.0 MAIN CONTENT

Traditional medicine and its use is rapidly increasing in industrialized and developing countries. In China, traditional herbal preparations account for 30% - 50% of the total medicinal consumption. In Ghana, Mali, Nigeria and Zambia, the first line of treatment for 60% of children with malaria is the use of herbal medicine at home. WHO estimates that in several African countries traditional birth attendants assist in taking care of births. In Europe, North America and other industrialized regions, over 50% of the population have used complimentary or alternative medicine at least once. The traditional medicine is referred to as complimentary or alternative medicine in industrialized countries. The global market for herbal medicines currently stands at over us $60 billion annually and it is growing steadily.

3.1 WHO Strategies on Traditional Medicine

WHO launched its first ever comprehensive traditional medicine strategy in 2002. This is in order to promote safe, effective and affordable traditional medicine practice. The strategy is designed to assist countries to:

1. Develop National policies on the evaluation and regulation of traditional medicine/complimentary or alternative medicine practices.
2. Create a stronger evidence base on the safety, efficacy and quality of the traditional medicine/complimentary or alternative medicine practice.
3. Ensure availability and affordability of traditional medicine/complimentary or alternative medicine including essential herbal medicines.
4. Promote therapeutically found use of traditional medicine/complimentary or alternative medicine by providers and consumers.
5. Document traditional medicines and remedies

3.2 Trial and Tested Methods and Products

1. 25% of modern medicines are made from plants first used traditionally.

2. Acupuncture has been proven effective in relieving post-operative pain, nausea and vomiting resulting from chemotherapy and dental pain with extreme effects. It can also alleviate anxiety, panic disorders and insomnia.

3. Traditional medicines have impact on infectious diseases. For example the Chinese herbal remedy *Artemisia annua,* used in China for almost 2000 years, has been found to be effective in resistant malaria and could create a breakthrough in

preventing almost one million people annually, most of them children, from severe malaria.

4. In South Africa, the Medical Research Council is conducting studies on the efficacy of Sutherland microphylla in treating AIDS patients. Traditionally used as a tonic, this increase energy, appetite and body mass in people living with HIV. Scientific evidence from randomized clinical trials is only strong for many uses of acupuncture herbal medicines and for some of the manual therapies. Further research is needed to ascertain efficacy and safety of several other practices and medicinal plants. Unregulated or inappropriate use of traditional medicines and practices can have negative or bad effects.

3.3 Policy on Traditional Medicine in Nigeria

Nigeria's quondam minister of Health, Professor Eyitayo Lambo informed the public on 14th September, 2002 that a draft of traditional medicine policy will be released soon". He said that the Health Ministry accords traditional medicine top priority because of the popularity of the practice among Nigerians". It is believed that Nigeria has more traditional healers than orthodox doctors who have education in Western Medicine. In 2007, twenty-five (25) pages of the Nigerian Traditional Medicine Policy were released with a mission to "create an enabling environment for the development of traditional medicine for national health system development and economic benefits."

Differences between traditional medicine and orthodox medicine

1. Traditional medicine is not well regulated by government while orthodox medicine is well regulated.
2. Traditional medicine is closer to people than orthodox medicine
3. Traditional medicine is usually cheaper than orthodox medicine
4. Traditional medicine practitioners sometimes make some mistakes which is uncommon with orthodox medicine.
5. To practice orthodox medicine one has to go through formal school which is not necessary in traditional medicine.
6. Dosages of drugs in orthodox medicine are well regulated and measured. It is not so with traditional medicine.

3.4 Traditional Medicine Practice in other African Countries

Uganda Health Ministry said that there is great popularity of traditional medicine healers estimating that two thirds of the country's inhabitants use their services regularly. On the 5th of February 2019, the Ugandan traditional medicine policy Act was passed. It seeks to regulate the use of complementary and traditional medicine in Uganda. The Act made provision for 20 million Shillings to be disbursed to herbalists and other providers of complementary/traditional medicine who advertise or operate unlicensed.

Nigeria and Uganda will be following South Africa law makers' efforts to make the traditional medicine sector safer for patients while at the same time raising its prestige. In South Africa traditional healers register with the government, giving them rights to treat diseases and discomforts even by issuing sick leaves. They are however barred from treating life-threatening diseases such as HIV/AIDS.

African governments hope to improve their control of the often chaotic informal health sector, where treatments are based on herbs and/or spiritual services. Some healers have been accused of putting their patients or others in danger, for example by urging AIDS patients to have unprotected sex with virgin girls. Regulation would open for control mechanism. This makes the practice risky for the populace. Nigerian Ministry of Health is paying "considerable attention to such areas as research and development" and co-operating with the National Institute for Pharmaceutical Research and Development (NIPRD).

SELF ASSESSMENT EXERCISE

Discuss the WHO strategies on traditional medicine

4.0 CONCLUSION

Since majority of our people, due to one reason or the other patronize traditional medicine practitioners a lot and the Government is aware of this, it is a wise decision for Government to give traditional medicine the needed attention that is giving it now but it should expedite action so that traditional medicine will also be regulated to guarantee more safety for the patients.

5.0 SUMMARY

In considering traditional medicine the following are important:

(1) Government should formulate National policy and regulation for the proper use of traditional medicine
(2) Establish regulatory mechanisms to control the safety, quality of products and practice of traditional medicine
(3) Create awareness about safe and effective traditional medicine therapies among the public
(4) Cultivate and conserve medicinal plants to ensure their sustainable use.

ANSWER TO SELF ASSESSMENT EXERCISE

WHO strategies on traditional medicine

1. Develop national polices on the evaluation and regulation of traditional medicine/alternative medicine
2. Create a stronger evidence base on safety, efficacy and quality of the traditional/alternative medicine
3. Ensure availability and affordability of traditional/altemative medicine including essential herbal medicines
4. Promote therapeutically sound use of traditional/altemative medicine by providers and consumer.
5. Document traditional medicines and remedies.

6.0 TUTOR-MARKED ASSIGNMENT

State the measures that Government can take to improve traditional medicine in Nigeria.

7.0 REFERENCES/FURTHER READINGS

http://www.afrol.com/articles/13950

http://www.who.int/mediacentre/factsheets/fsl34/en/

Traditional Medicine Policy for Nigeria. Mission statement. Page 8.

https://ncri.go.ug/document/the-traditional-and-complementary-medicine-act-2019/

UNIT 2 MEDICINAL PLANTS

CONTENTS

1.0 INTRODUCTION

Many Nigerians have embraced the use of botanicals and other supplements as a "a natural" approach to their healthcare. Unfortunately, misconceptions regarding safety and efficacy of the agents are common, and the fact that a substance can be called "natural" of course does not guarantee its safety. The medical use of botanicals in their natural and unprocessed form undoubtedly began when the first intelligent animals noticed that certain food plants altered particular body functions. Interest in the endocrine effects and possible nutritional benefits of certain purified chemicals, such as dihydroepiandrosterone, melatonin, high dose vitamins and minerals, has led to parallel development of consumer demand for such substances. These substances together with the botanicals constitute a substantial source of profits for those who exploit the concept of "alternative medicine". The alternative medicinal substances are usually available without prescription.

2.0 OBJECTIVES

At the end of the unit the learner will:
- understand what traditional medicine or alternative medicine is
- discuss the herbal medications presented in the lecture.

3.0 MAIN CONTENT

3.1 Garlic *(Allium sativum)*

Garlic contains a lot of organic sulphur compound. The most common one is allium which is responsible for the characteristic garlic odour. Garlic causes minor (5%) reductions in cholesterol which is insignificant when dietary controls are in place. Clinical trial report antiplatelet effects following its ingestion and mixed effects on fibrinolytic activity. These effects in combination with anti-oxidant effect and reductions in total cholesterol may be beneficial in patients with arteriosclerosis. Garlic constituents may affect blood vessel elasticity and blood pressure. Proposed mechanism include opening of potassium channels in vascular smooth muscle, stimulation of nitric oxide synthesis and inhibition of angiotensin converting enzyme. A meta-analysis of garlic's anti-hypertensive properties revealed a mild effect with a 7.7 mm Hg decrease in systolic pressure and 5mmHg decrease in diastolic pressure. The effect of garlic on glucose hemostasis is controversial, garlic has anti-microbial effect, *Allium* has demonstrated activity against gram positive and gram negative bacteria as well as fungi *(Candida albicans),* protozoa *(Entamoeba histolytica)* and certain viruses. The primary mechanism involves the inhibition of thiol containing enzymes needed by these microbes. Garlic has anti-neoplastic effects. In vitro garlic inhibits procarcinogens for colon, esophageal, lung, breast and stomach cancer probably by detoxification of carcinogens and reduced carcinogen activation. The evidence for anti-carcinogenic properties activity is largely epidemiological. Certain populations with high dietary garlic consumption appear to have a reduced incidence of stomach cancers.

3.2 Echinacea

The chemical constituents of Echinecea are flavonoids, lipophilic constituents, water-soluble polysaccharides and water-soluble caffeoyl conjugates e.g. echinacoside, chicoric acid, caffeic acid. Echinacea has immune modulation, anti-inflammatory effects and weak antibacterial, antifungal antiviral and antioxidant activities.

3.3 Fever Few (*Tanacetum Parthenium)*

Fever few contains flavonoid, glycosides, monoterpenes (e.g camphor, other pinene derivatives), and sesquiterpene lactones. The most prevalent sesquiterpene is pathenolide which is primarily found in the seeds and leaves of the plant, with concentrations ranging from 1% to 3%. Fever few is used for migraine headache and has anti-inflammatory effects.

3.4 Ginseng

Ginseng may be derived from any of several species of the genius panax. The active principles appear to be a dozen or more triterpenoid saponins glycosides called ginsenosides or panaxosides. Ginseng is most often used to help improve physical and mental performance.

Ginger

Ginger is the rhizome of *Zingiber officinale* (Roscoe), which has been scrapped and dried in the sun. It is grown in many parts of the world, including Jamaica, India and Africa. Ginger contains about 1-2 percent of volatile oil and 5-8percent of resinous matter, starch and mucilage. Oil of ginger, to which the drug mainly owes its aroma, contains terpenes, camphene and B - phellandrine, a sesquiterpene (Zingibene), cineole, cittal and borneol.

Uses: Ginger is used as a calminative and stimulant. It is more largely used as a condiment than as a drug.

Castor Oil Plant: Castor Oil is obtained from the seeds of *Ricinus communis.* The fruit is a three-celled, thorny capsules. It is cultivated in South America, various parts of Africa, Manchuria, Levant and Italy. The seed is oval, somewhat compressed from 8 to 18mm long and from 4 to 12mm broad. The testa is very smooth, thin and brittle.

Uses: Castor oil is widely used as purgative. Undecylenic acid which is prepared from castor oil is used in fungistatic preparations.

SELF ASSESSMENT EXERCISE

Discuss the uses of garlic.

4.0 CONCLUSION

Many medicinal plants have contributed a lot to the development of orthodox and traditional medicine. In orthodox medicine it gave rise to a branch of pharmacy called pharmacognosy.

5.0 SUMMARY

The medicinal plants in the units are garlic *(Allium sativum),* Echinacea *(Echinacea Purpurea),* fever few *(Tanacetum panthenum),* Ginseng, Ginger (*Zingiber officinale*) and castor oil plant. They all have various medicinal uses.

ANSWER TO SELF ASSESSMENT EXERCISE

Garlic has antihypertensive properties. It has antimicrobial properties. It also has antifungal, antineoplastic effects. It also has anticancer activities.

6.0 TUTOR MARKED ASSIGNMENT

Discuss the following medicinal plants

(i) Garlic,
(ii) Ginseng
(iii) Castor oil plant

7.0 REFERENCES/FURTHER READINGS

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