UNIVERSITY OF ILORIN
COLLEGE OF HEALTH SCIENCE
FACULTY OF BASIC MEDICAL SCIENCES
DEPARTMENT OF PHARMACOLOGY & THERAPEUTICS
PART I FINAL RESIT, JUNE 14, 2011

(6)

BOOKLET 1: SAQ 1 and LAQ 1
BOOKLET 2: SAQ 2
BOOKLET 3: SAQ 3
BOOKLET 4: SAQ 4
BOOKLET 5: SAQ 5 and SAQ 6
BOOKLET 6: LAQ 2 and LAQ 3
BOOKLET 7: LAQ 4

SHORT ANSWER QUESTIONS (SAQs) ANSWER ALL SIX (6)

LONG ANSWER QUESTIONS (LAQ'S) ANSWER LAQ 1 OR 2 and LAQ 3 OR 4

Don't forget to write your matriculation number and serial number on EACH booklet. AND INSIDE

WRITE THE ANSWERS IN THE CORRECT BOOKLET

LAQ 1 (booklet 1 IIII)

a. Briefly describe the pathological bass of schizophrenia
b. Describe the pharmacology of a named typical neuroleptic and one named atypical antipsychotic drug.
   Emphasis should be laid on the mode of action and toxicities of the two drugs chosen.

OR

LAQ 2 (booklet 6)

a. Classify drugs used in the treatment of systemic hypertension.
b. State concisely the exact mechanism of antihypertensive action of any two (2) of the classes.
c. Discuss the drug management of hypertension

LAQ 3 (booklet 6 IIII)

a. List and classify the current drugs used in the management of HIV/AIDS.
b. Outline the essential principles of the chemotherapy of AIDS. Discuss any three (3) of the principles.

OR

LAQ 4 (booklet 7)

a. Define the term Cancer Chemotherapy
b. Classify various anticancer chemotherapeutic agents currently in use.
c. Outline the various side effects associated with anticancer chemotherapy

SHORT ANSWER QUESTIONS

SAQ 1 (booklet 1)

Write briefly on the clinical indications for the use of any TWO of these drugs

a. Lidocaine
b. Propronalol
c. Hydralazine
d. hydrochlorthiazide

SAQ 2 (booklet 2)

Write briefly on the following:

a. Competitive antagonist
b. Quantal dose-effect curve
c. Volume of distribution of a drug (Vd)

SAQ 3 (booklet 3)

a. What is a prodrug
b. Write briefly on drug metabolism

SAQ 4 (booklet 4)

List five benefits of Pharmacogenomics

Write short notes on the clinical indications, mechanism of actions and adverse effects of ANY 2 of the following:

a. Rifampicin
b. Clofazamine
c. Amantadine

SAQ 5 (booklet 5)

a. List 3 examples of sympathomimetics and two clinical uses of each example.
b. Outline the steps at which drugs affect neurohumoral transmission.

SAQ 6 (booklet 5 !!!!)

a. List the advantages of Artemisinin-based combination therapy.
b. Write a short essay on the drug management of amoebiasis.

SAQ 1

a) Lidocaine

1) As a local anaesthetic agent

- Mechanism of action
  - * Blocks nerve conduction by inhibiting the voltage gated Sodium channels of the neuronal membrane
- Indications for local anaesthetics |SENSE|
  - * Surface anaesthesia * Nerve blocks * Spinal anaesthesia
  - * Epidural anaesthesia

2) As an anti-arrhythmic agent : Class IB

- Mechanism of action
  - * Blocks Na+ channels (I_{Na})
  - * Shortens phase 0 of the action potential
- Indication
  - * Treatment of ventricular arrhythmias especially post-myocardial infarction

b) Propanol — Class II

1) As an anti-arrhythmic agent

- Mechanism of action
  - * Reduction of sinus rate
  - * Reduction of conduction through the aorta

2) Treatment of thyroid storm

- Mechanism of action
  - * Management of the associated hypotension & tachycardia by decreasing cardiac output & blood pressure

c) Hydralazine

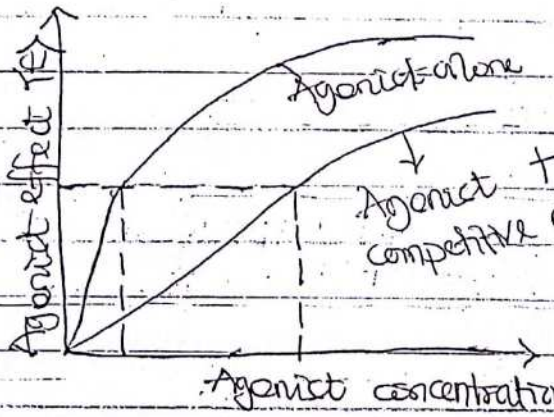
1) Treatment of moderate hypertension

- Mechanism of action
  - * Direct vasodilatation of extranodal smooth muscle which results in decreased peripheral vascular resistance

2) Treatment of congestive heart failure
- mechanism of action
Acts as a vasodilator which i) reduce preload (through vasodilation) ii) reduce afterload (through arterial dilation)

3) Hydrochlorthiazide
1) Treatment of congestive heart failure
- Mechanism of action:
i) Reduce preload: By minimizing salt & water retention
ii) Reduce afterload: By decreasing plasma volume
2) Treatment of nephrogenic diabetic insipidus
- Mechanism of action
Produces a slightly hyperosmolar urine & thus diminish polyuria

Q. 3
a) Competitive antagonist
- Introduction
* Reversibly competes with agonists for binding to receptors
* The maximal efficacy (Emax) for the agonist remains the same for any fixed concentration of antagonist but potency decreases
- Representation



- Interpretation
* In the presence of a competitive antagonist, higher concentration of agonist are required to produce a given effect and hence the curve is shifted to the right
(High agonist concentration can overcome inhibition by competitive

—Interpretation

* Drugs with very high Vd have much higher concentration in extravascular tissue than in the vascular compartment i.e. They're not homogenously distributed
* Drugs that're completely retained within the vascular compartment have a minimum possible Vd equal to the blood component in which they're distributed

SAQ 3

a) Prodrug

- A drug precursor
- A compound which on administration must undergo chemical conversion by metabolic processes before becoming an active pharmacological agent e.g. Cyclophosphamide, Lovastatin, Simvastatin, Fluoxetine, Isoniazid, Nalidixic acid, Sulfonamides, Aspirin

b) Drug metabolism

—Site of drug metabolism

* GIT * Skin * Kidneys
* Lungs * Brain

- Phases of metabolism

i) ~~Metabolism~~ Phase I

* Mixed function oxidases or monooxygenases are responsible and are located more in the microsomes
* Lipophilic molecules are converted into more polar molecules by the introduction (or unmasking) of a polar functional group
* Types of phase I reaction: (i) oxidation
(ii) reduction (dehydrogenation)
(iii) Hydrolysis

NB: Phase I is a non synthetic reaction
It prepares / readies products

* Site: Occurs principally in the liver
* Phase I reactions occur predominantly in the Cyt P450 system.

2) Phase II

* Involves formation of a covalent linkage between functi

groups on the parent drug and on the substrate.
* Substrates added: i) Glucuronate ii) Acetic acid iii) Glutathione iv) Sulfate
* In general, it follows phase I but in some cases, it precedes phase I. Once a drug completes from II, it is usually inactive. Both phase I & II rxn occur primarily in the liver. Factors affecting: Age & gender DDIs, especially in the induction of cytochrome P450 isoenzymes

Drug of choice

a) Rifampicin
—Clinical indications
1) TB prophylaxis in HIV patients
2) Prophylaxis of meningitis caused by Haemophilus influenzae and Neisseria meningitidis
3) Leprosy: In combination with Dapsone
4) Treatment of Legionnaires' disease: In combination with erythromycin
—Mechanism of action
* It inhibits the β-subunit of DNA-dependent RNA polymerase
* It suppresses RNA synthesis by blocking chain initiation
—Adverse effects
1) Urine, sweat, tears and other body secretions may become red-orange in colour
2) Rash, fever, nausea and vomiting are common
3) Flu-like syndrome with chills, fever & myalgias may develop in those who use it once or twice weekly

b) Clofazimine
—Clinical indication
i) Pharmacological treatment of leprosy: In combination with Dapsone & Rifampicin

Mechanism of action
It binds to DNA and inhibits its replication
Adverse effects
i) Distinctive reddish-brown discoloration of the skin
ii) GI irritation (nausea, vomiting, diarrhoea)

Amantadine - an indirect dopamine agonist
-Clinical indications
i) Treatment of Parkinson's disease

Mechanism of action
* Increases release & delays reuptake of dopamine in substantia nigra

Adverse effects
* Restlessness
* Bluish discoloration of the legs known as Livedo reticularis

→ Benefits of Pharmacogenomics (Pharmacogenomics is the study of the individual's genetic makeup to my or her response to specific drugs. It helps to identify genetic variations that cause differences in drug response among individuals in populations.)
ables doctors to prescribe drugs against diseases by observing individual's genetic makeup of the person & not just the symptoms of the ease

eases can be targeted easily by detecting the defected genes
lp in more efficient effect of drugs
ables drugs to be prescribed based on an individual's genetic
ike HP and not age & weight basis

EQ 5 5) Vaccines can be made with DNA & RNA without any risks

Examples of Sympathomimetics
i) Clonidine
* Treatment of hypertension especially in patients with renal disease
* Treatment of diarrhea in diabetic patients who have autonomic neuropathies.
ii) Dobutamine
* Treatment of unstable congestive heart failure
* Treatment of shock

Hi) A
* i)
Cardi
* H
the

ii) Step
→ Into
New
Impulse
of a
Peptide
→ Steps
i) Synth
2) Store
3) Relea
4) Recept
5) Inacti

Q) Exp
i) Low
Rece
* Re
follow
* As
Therefo
ii) Le

iii) Epinephrine
* Used in anaphylaxis & cardiac arrest to increase cardiac electrical activity
* Used in conjunction with local anaesthetics to prolong the duration of anaesthesia

5) Steps at which drugs affect neurohumoral transmission
→ Introduction
Neurohumoral transmission refers to the transfer of a nerve impulse from a presynaptic to a postsynaptic neuron by means of a humoral agent e.g. a biogenic amine, an amino acid, a peptide
→ Steps
1) Synthesis e.g. Levodopa, α-methyldopa
2) Storage e.g. Reserpine
3) Release e.g. Amphetamine, Guanethidine, clonidine
4) Receptor interaction e.g. α blockers, β-blockers
5) Inactivation of the transmitter

SAQ 6
a) List the advantages of Artemisinin-based combination therapy
i) Lower occurrence of recrudescence
Recrudescence:
* Re-occurrence of malaria symptoms within 3-4 weeks following treatment with artemisinin
* As a result of the short half-life of artemisinin, therefore small no of blood schizonts survive treatment
ii) To minimize resistance of plasmodium strains to them.

5) Drug treatment of amoebiasis

→ Introduction:

- Amoebiasis is a protozoal disease caused by Entamoeba histolytica

→ Drug treatment based on the following classification

i) Mixed / Extraluminal amebicides
- Effective against luminal & systemic disease
- Drug: metronidazole

ii) Luminal amebicides
- Effective only in the bowel lumen
- Drugs: * Diloxanide furoate
  * Paromomycin
  * Iodoquinol
  * Tetracycline

iii) Systemic amebicides
- Effective in the intestine & liver
- Drugs: * Emetine
  * Dehydroemetine
  * Chloroquine

AQ 1:

Briefly describe the pathological basis of schizophrenia

Introduction:

- Schizophrenia is a dysfunction characterized by

(a) positive symptoms: * Thought disorders
  * Delusions
  * Hallucinations (auditory)
  * Bizarre behaviour (aggressiveness & violence)

(b) Negative symptoms: * amotivation
  * Social withdrawal
  * Blunted emotions (emotional apathy)
  * Disruption of speech

- Pathological basis

* "Dopamine hypothesis of schizophrenia"
  - Schizophrenia is due to overactivity of dopamine in the mesolimbic dopamine system
  - Dopamine acts at various parts of the brain
  i) Advancement & reinforcement of the abnormal thought patterns in schizophrenia along with glutamate
  ii) Facilitates abnormal long term potentiation within the striatum, basal ganglia, cingulate gyrus & other limbic system structures

b)

Typical Neuroleptics	Atypical neuroleptic
-Chlorpromazine	Clozapine
~~Description~~ Introduction	-Mode of action
Prototype of the classical/ traditional neuroleptics	* Block D_4, 5HT$_2$ and D_2 receptors
-Mode of action	* Effective in managing both positive and negative symptoms
* A dopamine antagonist	
* Bind to D_1-D_5 types of dopaminergic receptors	
* Damage the positive symptoms	
Toxicities of both drugs	
1) On ANS	* Weight gain
-Blockade of α receptor	* Gynecomastia
2) On CNS	4) Effect on blood
- Parkinsonism	* Agranulocytosis : Clozapine
- Extrapyramidal effect	
* Akathisia	
* Acute dystonia	
3) Endocrine effect	
* Increased prolactin release leading to galactorrhea	
* Infertility	
* Impotence	

Q 2.

1) classification of drugs used in the treatment of systemic hypertension

1) Sympathetic agents
   - Centrally acting antihypertensives
     - Methyldopa
     - Clonidine → used in pregnant women. α_2 agonist.
     - Guanfacine
   - α blockers
     - Prazosin
     - Terazosin
     - Doxazosin
   - β blockers
     - Propanolol
     - Metoprolol
     - Atenolol
     - Labetalol
     - Carvedilol
   - Ganglionic blockers
     - Trimethaphan
     - Hexamethenium
   - Post-ganglionic neuronal blockers
     - Reserpine
     - Guanethidine

2) Diuretics
   - Thiazide : Hydrochlorothiazide
   - Loop : furosemide.

3) Vasodilators
- Hydralazine — oral
- Minoxidil — oral
- Sodium Nitroprusside — parenteral
- Diazoxide
- Calcium channel blockers — oral — verapamil, diltiazem, dihydropyridine, nifedipine

4) ACE inhibitors
- Captopril — Hypotensive
- Lisinopril — Teratogenic
- Enalapril — Angioedema
- Benazepril

5) Angiotensin II receptor antagonists
- Losartan
- Valsartan
- Candesartan
- Irbesartan

b) Mechanism of action

1) Angiotensin II receptor antagonists
- They block angiotensin II at its receptor site thus inhibiting both the vasoconstriction and aldosterone secreting effects of angiotensin II

2) ACE inhibitors
- They block the conversion of angiotensin I to angiotensin II and also increase levels of bradykinin which is a potent vasodilator

c)

Long management of hypertension

1) Hypertension: Give low dose thiazide diuretic
- If controlled: continue therapy
- Not controlled ↓

2) Add β-blockers: - controlled: continue therapy
- Uncontrolled: Go to No (3)

⇒ thiazide (diuretic)
↓
⇒ β blockers
↓
⇒ ACE I
↓
⇒ Add on for
↓
⇒ Ca channel blocker

Classification of various anticancer chemotherapeutic agents

1) Polyfunctional alkylating agents
- Bis(Chloroethyl)amines
* Cyclophosphamide
* Ifosfamide
* Chlorambucil
* Melphalan
- Nitrosoureas
* Carmustine (BCNU)
* Lomustine (CCNU)
* Semustine (methyl-CCNU)
* Streptozocin/Streptozotocin
* Triazines
* Thiotepa
* Altretamine
* Triethylenemelamine
* Alkyl sulfonates
Busulphan
Treosulfan
* Hydrazines
* Procarbazine
* Decarbazine
* Agents possibly acting as alkylating agents
- Platinum agents
Cisplatin
Carboplatin
Oxaliplatin
2) Antimetabolites
* Folic acid analogs/antagonists
* Methotrexate
* Pemetrexate
- Purine analogs/antagonists
* Mercaptopurine
* Thioguanine
* Azathioprine
* Cladribine
* Fludarabine
* Gemcitabine
- Pyrimidine analog/antagonists
- Fluorouracil
- Cytarabine
- Azacytidine
3) Natural products
(a) Plant alkaloids
- Vinca alkaloids
- Epipodophyllotoxins
- Taxanes
- Camptothecins
(b) Cytotoxic antibiotics
- Anthracyclines
- Actinomycins
- Others: Bleomycin, Plicamycine
(c) Enzymes: Asparaginase
(d) Biologic response modifiers
- Interferons
- Interleukins
4) Cytotoxic hormonal agents
- Androgens: Testosterone propionate
- Antiandrogens: Flutamide
- Oestrogens: Ethinyl oestradiol
- Antioestrogens: Tamoxifen
- Progestins: Medroxyprogesterone
- Adrenocortical compounds
- Gonadotropin releasing hormone agonists
- Aromatase inhibitor: Aminoglutethimide

CEFACLOR

- 2nd Generation cephalosporin
- Beta lactam antibiotic
- Inhibit transpeptidation rxn.
- orally
- Excreted by kidney
  - Ceftriazone } Excreted biliary
  - Cefoperazone }

Clinical indications:

⇒ H. influenza } Sinusitis
Moraxella Catarrhalis } otitis
} LRTI

Adverse Effect

- Allergic rxn

Ciprofloxacin (2nd generation fluoro

- fluoroquinolone group

- Blocks DNA Synthesis
  inhibit topo II & IV
  ↓ Prevent relaxation of coiled DNA
  ↘ interferes w/ separation.

- Bactericidal, wide distribution including brain & bone, high intracellular accumulation like PMN
- orally & IV, excreted by the kidney so adjustments for renal fxn
- clinical indication: UTI, GI CAP, MDR TB, Osteomyelitis, Anthrax, STD like Urethritis, Cervicitis

Toxicity: - GI upset
- Nephrotoxicity
- Tendinitis

Drug/Drug interaction; oral uptake competition with metal cations.

NB resistance to mut. in topo II
" " " IV (site for the gram -ve bacteria).
- Active efflux transport
- mult drug, plasmid mediated, recent discovery
- protection of topoisomerase II via Qnr protein
- Drug acetyl transferase modifying ciprofloxacin

NSAID

- Aspirin
- Ibuprofen
- piroxicam
- Naproxene
- Ketorolac — analgesic
- Indomethacin — antiinflammatory.

COX 1 — All cells

COX 2 = Inflammatory Cells.

Oxytocin

- peptide hormone.
- Important in labor & delivery
- used to eject milk

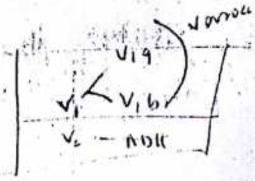
Pharmacokinetic

- IV = Induction & augmentation of labor.
  IM = post partum hemorrhage.

- No PPB
- Eliminated by renal & hepatic.
- ½ life = 5 mins

MOA

- Acts through G protein Couple receptor
- 2nd messenger phosphatidylinositol Calcium



⇒ Contract uterine Smooth muscle.

⇒ Stimulate release of prostaglandin & leukotriene.

⇒ activate Vasopressin Receptor V1

⇒ @ high Conc, it has weak antidiuretic Effect & Pressure ae

⇒ In small doses, it increase frequency & force of Contraction & high Dose it produce Sustained Contraction.

⇒ Contracts Myoepithelial cells in breast

Clinical uses

- Antipartum ← oxytocin challenge test
  ← Induce labor for condition requiring early vaginal deli
  ← Augment abnormal labor
- post partum: ⇒ Control uterine hemorrhage after CS delivery.
  ⇒ Induce abortion in 2nd trimester

Toxicity ⇒ i) fetal distress
ii) placenta Abruption
iii) uterine rupture

⇒ Hyponatremia
Heart failure
Seizure.

⇒ hypotension if given before