**Formative Assessment:**

### Single Best Answer Questions:

1. Which of the following statements concerning bioavailability and drug formulationis CORRECT?

(a) Bioavailability and bioequivalence are identical terms

(b) By definition, if a drug is administered orally it is said to have a bioavailability of 100%

(c) If two different formulations containing the same dose of the same drug have identical bioavailabilities then they will always show identical therapeutic effects

(d) The potential differences in bioavailability of various formulation of the same drug are most important with drugs that have a narrow therapeutic window or a small therapeutic index **T**

(e) A highly bioavailable drug will always have a short plasma half-life

*Bioequivalence relates to comparison of pharmaceutically similar compounds (e.g. brand vs generic product). To be bioequivalent, drugs will need to have similar bioavailabilities (how much active drugs is available at the relevant target).*

*Oral administration is unlikely to lead to 100% bioavailability as absorption from hostile GIT environment and first pass hepatic metabolism are likely to affect uptake.*

*Other factors in the drug formulation could potentially influence absorption/metabolism.*

*d) is correct since small changes in bioavailability of drugs with a small therapeutic window could be associated with more severe side effects/sub-therapeutic effects.*

2. Which of the following statements concerning acetylcholine is NOT correct?

(a) Is inactivated by re-uptake into nerves **T**

(b) Is released from pre-synaptic nerve terminals

(c) Increases peristalsis

(d) Can induce miosis (pin point pupils)

(e) Is inactivated by acetylcholinesterase

*Straightforward – Ach is broken down by acetylcholinesterase in the synapse not after reuptake.*

3. A section of vascular smooth muscle is placed in an organ bath and stimulated with increasing doses of noradrenaline. A graph of the relationship between dose and response (effect) wherein all possible degrees of response between minimum detectable response and a maximum response is produced. From the list below, please select which possibility could NEVER induce a maximal response.

(a) Noradrenaline plus Phentolamine (non selective α receptor antagonist)

(b) Adrenaline (agonist with lower affinity for α receptors)

(c) Clonidine (partial agonist) **T**

(d) Noradrenaline plus Propranolol (non selective β receptor antagonist)

(e) Phenylephrine (α1-selective agonist)

*Assuming noradrenaline is inducing vasoconstriction.*

*Maximal response is possible because;*

1. *The use of any competitive antagonist can be overcome by increasing the dose of agonist*
2. *Adrenaline still capable of acting on alpha receptors as a full agonist*
3. *NOT POSSIBLE – partial agonists cannot induce a maximal response*
4. *Beta blocker would have little effect on alpha mediated effect.*
5. *Phenylephrine is an alpha agonist*

4. Which of the following is NOT a recognised effect of anti-cholinesterase drug treatment?

1. Bronchdilation **T**
2. Hypotension
3. Increased secretions
4. Bradycardia
5. Pupillary constriction

*Straightforward – Anti-cholinesterase prevents Ach break down in the synapse so increases muscarinic effects. Muscarinic effect in the lung is bronchoconstriction.*

5. Which of the following drugs is NOT an adrenoceptor antagonist ?

1. phentolamine
2. methyldopa **T**

(c) propranolol

1. prazosin
2. atenolol

*Straightforward – Just need to know your drugs.*

6. Glaucoma of all types is estimated to affect more than 1% of the population over the age of 40 years. Various pharmacological approaches are available for the treatment of glaucoma during an acute attack. Which of the following drugs types should NOT be used to treat glaucoma?

1. Cholinergic/parasympathetic-agonist
2. Anticholinergic/antimuscarinic/parasympathetic-antagonist **T**
3. Sympathetic-agonist/sympathomimetic
4. β-adrenoceptor blocker
5. Carbonic anhydrase inhibitors

*Pupillary constriction (via muscarinic receptors) open the venous drainage channels to facilitate the drainage of aqueous humour. A) would have a positive effect on this, b) a negative effect. C) cause vasoconstriction and reduce blood flow to the eye thus decreasing aqueous humour production. Aqueous humour production is also inceased via a beta mediated increase in carbonic anhydrase activity so d) and e) would also help.*

7. A 54-year-old man is admitted to Accident & Emergency suffering an anaphylactic reaction after being stung by a wasp whilst out rambling. The registrar finds a bottle of β-blocker tablets in his pocket. Which of the following clinical features of anaphylaxis could be worsened by these tablets?

(a) Bronchospasm & Hypertension

(b) Bronchospasm alone **T**

(c) Hypertension alone

(d) Bronchospasm & Hyperglycaemia

(e) Hypertension & Hyperglycaemia

*Beta mediated effects that would help alleviate anaphylaxis are bronchodilation and increased HR/force of contraction. Not a brilliantly written question as hypertension and hyperglycaemia are NOT clinical features of anaphylaxis!*

8. Which of the following statements concerning anaphylaxis is NOT correct?

1. can be treated by an injection of noradrenaline **T**
2. involves respiratory difficulty and/or hypotension
3. is a systemic allergic reaction
4. requires previous exposure to the antigen
5. is a type 1 hypersensitivity response

*Another anaphylaxis question that is not brilliantly written. You would see some improvement with an injection of noradrenaline, but adrenaline is the better option by far.*

**Multiple Choice Questions:**

*This format isn’t in the exam, but is in the study guide to help you check your knowledge.*

**1. Dihydropyridine calcium channel blockers:**

A. inhibit calcium entry via the sodium calcium exchanger **F**

B. slow heart rate **F**

C. cause arterial vasodilation **T**

D. cause swollen ankles **T**

E. prolong bleeding time **F**

**2. Increased parasympathetic activity in the cardiovascular system;**

A. increases heart rate **F**

B. decreases beat to beat variability  **F**

C. decreases the risk of cardiac arrhythmias **T**

D. may occur during fainting (syncope) **T**

E. is reversed by atropine **T**

**3. Beta blockers are useful in angina because they;**

A. reduce heart rate **T**

B. cause vasoconstriction **F**

C. cause upregulation of alpha adrenoceptors **F**

D. decrease venous return **F**

E. reduce the incidence of sudden death **T**

# 4. Streptokinase

1. Activity can be diminished by previous streptococcal infection**T**
2. Activates plasminogen **T**
3. Is contraindicated in patients with peptic ulcer **T**
4. Prevents fibrin accumulation **F**
5. Improves outcome in DVT **F**

# 5. Warfarin

1. is administered intravenously **F**
2. activity is monitored by means of APTT **F**
3. effects can be reversed by Vitamin K **T**
4. is used in the treatment of acute MI **F**
5. activity affects only the extrinsic pathway of coagulation **F**

### 6. Dobutamine

1. is a long acting oral preparation **F**
2. may be used to treat acute heart failure **T**
3. has negligible effects on peripheral vasculature **T**
4. is useful in the treatment of asthma **F**
5. may be used to treat threatened, uncomplicated premature labour **F**

**7. Inflammation in atherosclerosis;**

A. is important only in the early stages of the disease **F**

B. may be associated with modified LDL particles **T**

C. may be suppressed by statins and fibrates **T**

D. mainly involves neutrophils **F**

E. is usually best reflected by erythrocyte sedimentation rate (ESR) **F**

# 8. Aspirin;

A. reversibly inhibits cyclooxygenase enzymes **F**

B. increases bleeding time **T**

C. can induce bronchospasm **T**

D. increases the activity of heparin **F**

E. induces thromboxane A2 synthesis **F**

**9. Anaphylaxis;**

1. can be treated by an injection of noradrenaline **F**
2. involves respiratory difficulty and/or hypotension **T**
3. is a local allergic reaction **F**

D. requires previous exposure to the antigen **T**

E. is a type 1 hypersensitivity response  **T**

1. **Thiazides;**

A. are used in the treatment of hypertension **T**

B. exert diuretic effects which are due mainly to blockade of carbonic anhydrase **F**

C. promote K+ excretion **T**

D. often cause hypoglycaemia **F**

E. are useful in the treatment of heart failure **T**

1. **Morphine**

* Is used mainly for the control of mild to moderate pain **F**
* Causes pupil constriction **T**
* Is always given intravenously **F**
* Acts only on µ opioid receptors **F**
* When given repeatedly may cause constipation **T**

1. **Opioid drugs**

* Include methadone **T**
* Cause respiratory depression **T**
* Act via intracellular receptors **F**
* Normally excite their target cells **F**
* Are drugs of abuse **T**

1. **Repeated administration of opioids**

* Results in the development of tolerance **T**
* Is associated with a marked increase in the rate of opioid metabolism **F**
* Does not cause psychological dependence **F**
* Causes physical dependence which is satisfied by the administration of mu opioid receptors agonists **T**
* Is of no value in the control of chronic pain **F**

1. **Heroin (diamorphine)**

* Is a more powerful analgesic drug than codeine **T**
* Is used in preference to pethidine in obstetrics **F**
* Causes euphoria and sedation **T**
* Produces effects which are antagonised by naloxone **T**
* Is degraded by peptidase enzymes **F**

**15. Cocaine;**

1. has local anaesthetic properties **T**
2. can induce miosis (pin point pupil) **F**
3. enhances sympathetic transmission by inhibiting uptake 1 **T**
4. can cause euphoria **T**
5. can only be administered by the intravenous route **F**

**16. Ethanol;**

1. can induce cutaneous vasoconstriction **F**
2. can induce a pseudo-Cushing’s syndrome **T**
3. has an anti-diuretic effect **F**
4. acts as a CNS depressant **T**
5. can protect against ischaemic heart disease **T**

**17. Regarding ethanol metabolism**

1. Asian races possess genetic variations in the enzyme aldehyde dehydrogenase associated with alcohol intolerance **T**
2. Asian races possess genetic variations in the enzyme alcohol dehydrogenase associated with alcoholism **T**
3. 25% of ethanol is metabolised extra-hepatically **F**
4. Acetate is a toxic end-product of ethanol metabolism **F**
5. Disulfiram enhances ethanol metabolism **F**

**18. Concerning Parkinson’s disease;**

1. COMT inhibitors can be used to increase the bioavailability of L-DOPA. **T**
2. L-DOPA is given in combination with a peripheral DOPA decarboxylase inhibitor to prevent its peripheral conversion to dopamine. **T**
3. Deprenyl (selegiline) is a selective mono- amine oxidase-A (MAO-A) inhibitor. **F**
4. Bromocriptine is a dopamine D2 receptor antagonist. **F**
5. Nausea, one of the acute side-effects of L-DOPA, can be treated using domperidone, a peripherally acting dopamine receptor antagonist. **T**

**19. Neuroleptic drugs;**

1. are used to treat schizophrenia **T**
2. produce their beneficial clinical effects by antagonising dopamine D1 receptors **F**
3. produce extensive side effects due to their antagonism at other receptors **T**
4. stimulate nausea and vomiting **F**
5. also increase serum prolactin levels that can lead to breast swelling **T**

**Short Answer Questions:**

1. A male and female of exactly the same weight are given exactly the same oral dose of alcohol (ethanol) after fasting overnight.

1. The graph below represents the blood alcohol concentrations over 4 hours after this oral dose of ethanol was given to the MALE volunteer described above.

Time (h)

1

2

3

4

10

20

30

40

50

60

70

80

Blood ethanol

(mg/100ml)

i) Draw on the graph above what you would expect to happen after this oral dose of ethanol was given to the FEMALE volunteer described above.

*Paralell (1 mark) shift upwards (1 mark)*

***(2 marks)***

1. Please give your reasoning for your answer in part i)

***Either****; Males have more body water per kg (1 mk), so alcohol is more diluted in the body i.e. less in blood (1 mk)* ***Or;*** *Females have more body fat per kg (1 mk), and alcohol doesn’t penetrate adipose tissue as well i.e more in blood (1 mk)* ***Or;*** *Males have more alcohol dehydrogenase (1mk) so alcohol is metabolised faster (1 mark)*

***(2 marks)***

1. Consider the graph in part (a), representing the blood alcohol concentrations over 4 hours after the oral dose of ethanol was given to the MALE volunteer.
2. Describe how the response would differ if the MALE volunteer had been given a large meal BEFORE the oral dose of ethanol had been given.

*Shift downwards (1 mark) but slightly prolonged blood clearance (1 mark)*

***(2 marks)***

1. Please give your reasoning for this answer (include reference to alcohol metabolism in your answer).

*Food in the stomach slows absorption (1 mk), lower portal vein concn and∴ liver enzymes (1st pass hepatic clearance) are less saturated (1 mk) & less unmetabolised ethanol reaches systemic circulation* ***(2 marks)***

1. State the two enzyme/enzyme systems in the liver that convert ethanol to acetaldehyde.

*Alcohol dehydrogenase & mixed function oxidase*

***(2 marks)***

**2.**

a) Describe the principal mechanisms by which (i) morphine and (ii) aspirin induce analgesia

Morphine -

*Morphine impairs pain perception (nociception) [½ mark] by acting on specific opioid receptors [½ mark] in the spinal cord and brain [½ mark] to suppress afferent transmission in the pain pathways directly and by augmenting the ‘gating’ mechanism [½ mark]. It may also exert additional inhibitory effects on nociceptive*  *afferent nerve terminals in the periphery [½ mark].*

*Morphine also has a euphoric action which augments pain tolerance [½ mark].*

Aspirin -

*Aspirin acetylates and thereby causes irreversible [½ mark] inactivation of cyclo-oxygenase [½ mark], the enzyme which is required for the conversion of arachidonic acid into prostanoids [½ mark]. As prostaglandins released at the site of injury, infection or inflammation sensitise sensory nerve endings to pain-inducing substances (e.g. kinins, 5HT), aspirin exerts an analgesic action [½ mark].*

***(5 marks)***

b) Describe the main effects of long-term use of (i) morphine and (ii) aspirin on the gastrointestinal tract

Morphine -

*Morphine slows gastric emptying, reduces gastrointestinal motility and impairs water absorption [½ mark] together these cause constipation [½ mark]. (It also increases pressure in the biliary tracts and may thereby cause pain in subjects with gall stones).*

Aspirin -

*Aspirin - gastric irritation [½ mark] and high risk of gastric bleeding [½ mark]. Patients complain of dyspepsia, diarrhoea (sometimes constipation), nausea and vomiting.*

***(2 marks)***

c) When given in high doses both morphine and aspirin produce potentially fatal effects.

i) Explain what steps may be taken to overcome such actions of morphine

*Intravenous administration of an opioid receptor antagonist [½ mark] such as naloxone [½ mark].*

***(1 mark)***

ii) Explain why an alkaline diuresis forms an important part of the treatment regime in conditions of acute aspirin poisoning

*Aspirin is a weak acid (pKa appox 3.6 )[½ mark]. By making the urine alkaline (sodium bicarbonate load), the degree of ionisation of aspirin in the tubular fluid will be increased [½ mark]. As the ionised form is not readily reabsorbed, it will pass through the tubule to the bladder [½ mark]. An alkaline diuresis will therefore reduce aspirin toxicity by accelerating the excretion of drug [½ mark].*

***(2 marks)***

3. There are many routes by which medicines may be administered to a patient but the oral route is the most common and convenient.

(a). List three advantages shown by the oral route.

*Three of the below...*

*it permits self-medication*

*it does not require rigorously sterile preparations*

*the incidence of anaphylactic shock is lower (than intravenous)*

*there is the capacity to prevent complete absorption (vomiting, lavage)*

***(3 marks)***

(b). However, the oral route also has certain disadvantages. List two of these disadvantages.

*Two of the below...*

*it is inappropriate for drugs that are labile in acid pH of stomach or otherwise degraded*

*it is inappropriate for drugs that undergo extensive ‘first-pass’ effect*

*it requires patient compliance*

***(2 marks)***

(c). Many different types of formulation may be used to deliver a drug via the oral route. List two of these.

*Tablet, caplet, capsule, soluble tablet, soluble powder, syrup, linctus, elixir(?), etc*

***(2 marks)***

(d) During its absorption from the gastrointestinal lumen to its entry into the systemic circulation a drug has to pass several obstacles that may inhibit its journey. List three of these potential hazards.

*Three of the below...*

*physicochemical interaction between drug and gut contents*

*chemical degradation in acid of stomach or via enzymes*

*metabolism in gut wall*

*metabolism within the liver*

*excretion via the bile*

***(3 marks)***

**4.**

a) Name two types of nerve terminal in the autonomic nervous system where acetyl choline

acts as a neurotransmitter.

*Any two of:*

*All preganglionic neurones*

*All postganglionic parasympathetic neurones*

*Sympathetic supply to the adrenal medulla*

#### The postganglionic sympathetic supply to the sweat glands (1 mark each)

*NO MARKS for the NMJ because this is not ANS!*

***(2 marks)***

b) In the airways, acetylcholine mimics the action of which nerve?

## Vagus (Xth) *(1 mark)*

c) What are the actions of muscarinic antagonists on the following;

1. the heart? *Modest tachycardia 1 mark*

ii) the gastrointestinal tract? *Inhibition of motility 1 mark*

iii) the eye? *Dilated pupil, paralysis of accommodation, poss rise in intraocular pressure 1 mark*

***(3 marks)***

1. Irreversible blockade of acetylcholine breakdown produces potentially fatal respiratory depression. Explain how actions at the following sites compromise respiration.

Lungs –

*Build up of acetylcholine at muscarinic synapses in the lung (1 mark)*

*causes bronchoconstriction and increased bronchial - 1 mark*

*(If students state that effects reinforced by build up of acetylcholine at nicotinic synapses of the parasympathetic ganglia, a mark can be given, but only up to a total of 2 marks)*

***(2 marks)***

Neuromuscular junction –

*Build up of acetylcholine at the nicotinic synapses at the skeletal neuromuscular junction (1 mark) leads to initial twitching and subsequent paralysis of the diaphragm and respiratory muscles – 1 mark*

***(2 marks)***

**5.**

a) Give an example of the following β-Adrenoceptor antagonists

Non-selective - *Propranolol*

Cardioselective - *Atenolol*

***(2 marks)***

b) Beta-adrenoceptor antagonists can be used to treat hypertension. State two effects of these drugs which lead to a fall in blood pressure and explain the mechanism for each.

*Blockade of beta-1-receptors (1/2 mark) has negative chonotropic and inotropic effects (1/2 mark). This slows conduction through the AV node (1/2 mark) and reduces cardiac output (1/2 mark),*

***(2 marks)***

*Reduced angiotensin II production (1/2 mark) via reduction of renin release (1/2 mark) by competitive antagonism of beta-1-receptors (1/2 mark) in the kidney (1/2 mark).*

***(2 marks)***

c) Name the predominant adrenoceptor sub-types present in i) cardiac muscle, ii) vascular smooth muscle of blood vessels supplying the skin, iii) vascular smooth muscle of blood vessels supplying skeletal muscle and iv) bronchial smooth muscle and describe the consequences of activation of the sympathetic nervous system on these tissues.

1. *β1 – increased rate and force of contraction; increased cardiac output*
2. *α1 – constriction; increased peripheral resistance*
3. *β 2 – dilatation; reduced peripheral resistance*
4. *β 2 – relaxation; reduced airways resistance*

***(4 marks)***

6.

a) Explain the molecular mechanism by which aspirin exerts its analgesic actions

*Stimulation of PG receptors on sensory nerve endings lowers the threshold for perception of pain (they are hyperalgaesic) (1/2 mark). Aspirin irreversibly inhibits COX (1/2 mark), the rate limiting enzyme for prostanoid synthesis (1/2 mark). By preventing PG synthesis, it prevents sensitization of nociceptors and the threshold for pain is increased (1/2 mark).*

***(2 marks)***

b) Aspirin also has an anti-aggregatory action against platelets. Explain how this occurs.

*TXA2 made by platelets is pro-aggregatory (1/2 mark). Aspirin prevents its synthesis by COX inhibition. Because the inhibition is irreversible and the platelet has no nucleus (1/2 mark), the effect lasts until new platelets are synthesized. Synthesis of anti-aggregatory PGI2 (prostacylin) by endothelial cells is also inhibited by aspirin (1/2 mark) but the effect is short lasting because endothelial cells synthesize new enzyme (1/2 mark)*

***(2 marks)***

c) Why is this anti-aggregatory effect not displayed by other non-steroidal anti-inflammatory drugs (NSAIDS)?

*Other NSAIDS are reversible, so the TXA2 synthetic pathway rapidly recovers (1 mark). NO mark for saying that aspirin inhibits COX1 and other NSAIDS inhibit COX2 – they are not that specific!*

1. ***mark)***

d) Why is paracetamol not classed as an NSAID?

*It has no anti-inflammatory activity*  ***(1 mark)***

1. What is the most serious side-effect of paracetamol in overdose?

*Hepatotoxicity*  ***(1 mark)***

1. Explain the mechanism by which this unwanted effect occurs

*A reactive, but minor metabolite ( ½ mark) of paracetamol, (N-acetyl-p-benzoquinoneimine) is normally safely conjugated with glutathione ( ½ mark). At high concentrations of drug, glutathione is depleted ( ½ mark) and the metabolite oxidises thiol groups of key hepatic enzymes and causes cell death ( ½ mark)*

*Don't penalise students if they don't name the metabolite – the principle is the important point*  ***(2 marks)***

1. What antidote specific to paracetamol overdose would you give?

*Intravenous acetylcysteine: total of 300 mg/kg over 20h*

*Oral methionine (rarely used): 10 g over 12h (1 mark for either)* ***(1 mark)***