APPLIED THERAPEUTICS OF THE CENTRAL NERVOUS SYSTEM

PHA-MFB2

Time allowed: 2 hours

Part ONE

Answer ALL questions. For each question, there is ONE correct answer. Use the answer grid provided for ALL your answers.

Part TWO

Answer TWO of the THREE questions. Use a SEPARATE answer book for EACH question in Part TWO.

All questions have equal weighting. Answer ALL parts of each of the individual questions you select.

The mark allocation for the paper is:
- Part ONE carries 50% of the total mark
- Part TWO carries 50% of the total mark

This paper consists of 13 pages in total.

The following is provided: Multiple choice answer grid.

Dictionaries are not permitted in this examination.

Notes are not permitted in this examination.

Do not turn over until you are told to do so by the Invigilator.

Do not take this question paper out of the examinations room.
PART ONE
SECTION A – TYPE 1 MCQ

Answer ALL questions. For each question there is ONE correct answer. Use the answer grid provided for ALL your answers.

1. Which ONE of the following is NOT a key feature of the blood-brain barrier?
(A) A three cell architecture comprising the brain microvascular endothelia, astrocyte foot processes and pericytes.
(B) A highly restrictive paracellular barrier
(C) A high density of capillary fenestrations
(D) A high density of efflux transporter expression
(E) A relatively low density of endocytic vesicles

2. Which ONE of the following physicochemical drug parameters would be MOST LIKELY associated with low blood-brain barrier penetration?
(A) A log P_{octanol/water} of 3.5
(B) A polar surface area of 125 Å²
(C) An affinity for an amino acid uptake transporter
(D) No affinity for the ABCB1 ATP-binding cassette transporter
(E) A low number of hydrogen bonding groups

3. Which ONE of the following is INCORRECT regarding the enzyme GABA transaminase?
(A) It is inhibited by vigabatrin
(B) GABA is a substrate
(C) Glutamate is a product
(D) Its activity decreases the concentration of glutamine in astrocytes
(E) Its activity decreases the concentration of GABA in the synaptic terminal

4. Which of the following is NOT being investigated as a drug discovery target for Alzheimer’s disease?
(A) N-Methyl D-aspartic acid (NMDA) receptor
(B) Histone deacetylase (HDAC) inhibitors
(C) Proton pump inhibitors
(D) β-secretase (BACE) inhibitors
(E) Phosphodiesterase 5 (PDE5) inhibitors
5. What is the potential benefit of antibodies that target amyloid-β (Aβ) peptide?

(A) Decreased cleavage of the precursor protein by β-secretase
(B) Increased cleavage of the precursor protein by γ-secretase
(C) Increased aggregation of amyloid-β (Aβ) peptide
(D) Increased clearance of amyloid-β (Aβ) peptide
(E) Increased activation of apolipoprotein E (ApoE)

6. Why does L-DOPA pass the blood-brain barrier whereas dopamine does not?

(A) L-DOPA is significantly more lipophilic than dopamine
(B) L-DOPA is taken up by active transport
(C) L-DOPA passes the blood-brain barrier as a protein conjugate
(D) L-DOPA undergoes Phase II glucuronidation and the glucuronide passes the barrier
(E) L-DOPA is neutral at physiological pH whereas dopamine is positively charged

7. What class of molecule is phenazocine an example of?

(A) An oripavine
(B) A benzomorphan
(C) A morphinan
(D) A 4-phenylpiperidine
(E) An opioid

8. Select the correct answer relating to the biosynthetic pathway for the preparation of opioids.

(A) Thebaine is a precursor of codeine
(B) Codeine is a precursor of reticuline
(C) Morphine is a precursor of papaverine
(D) Papaverine is a precursor of thebaine
(E) Thebaine is a precursor of reticuline
9. Which **ONE** of the following patients would be classified as a ‘migraineur’ according to the International Headache Society (IHS) classification?

(A) A patient with four attacks of headaches, lasting for 24 hours that throb and are aggravated by movement. They also suffer from a dislike of bright lights and noise during the attack but no other symptoms

(B) A patient with six attacks of headaches, lasting 36 hours that start on one side of the head, throb and are severe in intensity. They have no other symptoms

(C) A patient with eight attacks of headaches, lasting 86 hours that are aggravated by activity and severe in intensity. They also suffer from nausea and vomiting during the attack, but no other symptoms

(D) A patient with ten attacks of headaches, lasting 48 hours that are moderate severity. They also suffer from vomiting and photophobia during the attack, but no other symptoms

(E) A patient with twelve attacks of headaches lasting 72 hours, on one side of the head and throbbing. They also suffer from nausea and vomiting during the attack, but no other symptoms

10. Neuropathic pain is severe, chronic pain which can be associated with stroke, multiple sclerosis, diabetic neuropathy and limb amputation. Which **ONE** of the following statements about neuropathic pain is correct?

(A) Neuropathic pain responds well to treatment with classic analgesic drugs

(B) Tricyclic antidepressants can be effective

(C) Neuropathic pain is a protective mechanism

(D) Gabapentin can be used in treatment and is thought to work on voltage-gated K channels

(E) Diabetic patients develop neuropathic pain as a result of insulin

11. Pain can be defined as an unpleasant sensation perceived from a specific location in the body. Which **ONE** of the following statements about nociceptors is INCORRECT?

Nociceptors are:

(A) Polymodal

(B) Only present on unmyelinated C fibres

(C) Activated by heat

(D) Activated/sensitised by chemical mediators

(E) Involved in activating ascending pathways to the cerebral cortex
12. Following trauma or tissue damage nociceptive afferent terminals receive noxious information through activation of ion channels. Which ONE of the following combinations of mediator and channels is INCORRECT?

(A) Capsaicin and endovanilloids activating NaV1.7 to cause depolarisation
(B) ATP activating P2X channels to cause depolarisation
(C) Heat activating TRPV1 channels causing Na\(^+\) and Ca\(^{2+}\) influx
(D) Prostaglandin E acting on EP receptors to sensitise/activate NaV channels
(E) Cold temperatures activating TRPM8 causing depolarisation

13. Mr JM is a methadone user and is admitted to hospital with a psychotic episode. The duty doctor cannot confirm Mr JM’s methadone dose but notices on a previous admission that Mr JM was prescribed 50 mg daily. The doctor writes the prescription for methadone 50 mg daily.

What action should the doctor have taken before writing the prescription?

(A) Confirmation must be made that Mr JM is opiate positive with a urine screen
(B) The doctor should ask Mr JM about his dose of methadone
(C) The doctor should prescribe an initial dose of methadone between 10-30 mg
(D) The methadone dose should be titrated against withdrawal symptoms
(E) The methadone prescription should be delayed until Mr JM’s psychotic episode has resolved

14. Mrs SB is taking 80 mg methadone daily by supervised consumption. She has failed to collect her methadone prescription for 3 days. On the 4\(^{th}\) day she appears in your pharmacy apologising. She said that she has been away and managed to buy some methadone off friends.

(The prescription does comply with home office wording which allows your discretion to supply if doses are missed).

She stated that she will be fine to have her 80 mg dose, what do you do?

(A) She is clearly NOT withdrawing so you give her the 80 mg dose
(B) Patients who have missed 3 or more doses might be at risk of reduced tolerance and you should contact her key worker for advice
(C) You suggest that she continues seeking to buy methadone until she sees her key worker
(D) You give her a reduced dose of 50 mg as her tolerance has been reduced
(E) You split her methadone dose 40 mg twice daily supervised to make sure she is not over sedated
15. 6-APB is an analogue of which illicit drug?

(A) Cocaine  
(B) LSD  
(C) Snuff  
(D) DMT  
(E) Ecstasy

16. Miss SM a 27 year old lady, who is a regular customer at your community pharmacy tells you that for the past few days she has been experiencing a sore throat, fever and mouth ulcers. You see from her PMR that she was started on phenytoin 100mg twice daily 2 weeks ago and she asks if these symptoms could be due to her new medication. What would be the most appropriate advice to give Miss SM?

(A) The symptoms described are NOT known to be caused by phenytoin  
(B) She should see her GP as the dose of phenytoin needs to be increased  
(C) She should see her GP as the dose of phenytoin needs to be reduced  
(D) She’s experiencing a side effect of her phenytoin, and whilst safe to take it she may want to see her GP to discuss an alternative  
(E) She should see her GP straight away as the phenytoin needs to be stopped and an alternative therapy started

17. Mr JS has recently been diagnosed with epilepsy following a number of seizures. He asks you whether he is able to drive his car. Which of the following would be appropriate advice for the patient?

(A) He should abstain from driving for the next 10 years  
(B) He should abstain from driving until he has started his anti-epileptic drugs  
(C) He may drive a car, though should not drive a motorcycle or a heavy machinery  
(D) He should abstain from driving until he is seizure free for 1 year  
(E) He should abstain from driving until he has been on his anti-epileptic drugs for 1 year

18. Which ONE of the following statements is NOT true about valproic acid?

(A) It is formulated as the sodium salt  
(B) It increases levels of the neurotransmitter GABA  
(C) Its antiepileptic properties were discovered by accident  
(D) It can inhibit histone deacetylases  
(E) It is mainly inactivated by Phase I metabolism
19. In the treatment of glaucoma, which drug classes should be avoided in patients with asthma?

(A) $\beta$-blockers AND $\alpha_2$-agonists
(B) Prostaglandin analogues AND $\alpha_2$-agonists
(C) $\beta$-blockers AND muscarinic agonists
(D) Prostaglandin analogues AND muscarinic agonists
(E) Carbonic anhydrase inhibitors AND $\beta$-blockers

20. Which ONE of the following is INCORRECT regarding the “conventional pathway” for outflow of aqueous humor in the human eye?

(A) The majority of aqueous humor leaves the eye via this pathway
(B) This pathway involves the passage of aqueous humor through the trabecular meshwork
(C) This pathway involves the passage of aqueous humor through the Canal of Schlemm
(D) This pathway is also referred to as the “uveoscleral pathway”
(E) This pathway involves drainage of vitreous humor via the “angle” between the cornea and the iris
SECTION B – EXTENDED MATCHING MCQ

Answer ALL questions. For each question there is ONE correct answer. Use the answer grid provided for ALL your answers.

For the drug attributes described, select the correct molecule from the list of anti-Parkinson drugs below.

21. A drug that acts as an agonist at the dopamine receptor

22. A drug that is designed not to penetrate the blood-brain barrier

23. A drug that inhibits the breakdown of dopamine
For the patients described, select the most appropriate choice of drug from the list below.

Each option may be used once, not at all or more than once.

(A) Ibuprofen
(B) Aspirin
(C) Diamorphine
(D) Buprenorphine
(E) Codeine
(F) Gabapentin
(G) Methadone

24. Mr SY, a 79 year old man who has been diagnosed with acute gout.

25. Mrs DY, a 60 year old lady with a previous medical history of type 1 diabetes mellitus has had a lower left leg amputation. She has been experiencing significant phantom limb pain.

26. Mrs YR, a 27 year old lady has fractured her left leg, following a skiing accident. She is currently taking naproxen and paracetamol for pain relief, though is still in significant pain. The GP wants to add in another analgesic.

27. Mrs IY, a 66 year old lady is a palliative breast cancer patient. The GP wants to start her on a subcutaneous syringe driver for pain relief.
For the patients described, select the most appropriate medication from the list below.
Each option may be used once, more than once, or not at all.

(A) Buprenorphine  
(B) Dihydrocodeine  
(C) Lofexidine  
(D) Methadone  
(E) Diazepam  
(F) Naltrexone  
(G) Naloxone

28. Mr BE is a known heroin user and has been ‘in and out’ of prison for his drug related behavior. He has also over dosed on heroin twice but friends managed to get him to A&E in time. He is discussing his options with his keyworker and wants to know which medication would now be suitable as a replacement for his heroin misuse?

29. Mrs SL is taking methadone 20 mg daily and would like to undergo a home opioid detoxification. She is planning on reducing methadone by 5 mg each week. Her key worker will visit daily with medication to help her with opiate withdrawals. Sophie has normal baseline blood pressure and pulse.

30. Mrs AB has undergone an opiate detoxification through your pharmacy and is concerned she might relapse into using opiates again. She asks you if there is any medication she could take to help her to abstain from opioid misuse.
PART TWO

Answer TWO of the THREE questions. Use a SEPARATE answer book for EACH question.

31. Answer ALL parts (a) to (d).

Rivastigmine is used in the treatment of both Alzheimer’s and Parkinson’s disease.

(a) With the aid of suitable diagrams discuss the aetiology of Parkinson’s disease. [50%]

(b) Using diagrams and chemical structures, describe how rivastigmine interacts with its molecular target. In your answer discuss the physiological consequences of this interaction. [30%]

(c) Suggest why rivastigmine has relatively few drug-drug interactions. [10%]

(d) Show reagents and reaction conditions for the synthesis of rivastigmine from the intermediate below. [10%]
32. Answer ALL parts (a) to (c).

(a) Mr JZ has been regularly using OTC codeine based pain killers for migraine headaches. Outline the potential problems with this approach and the advice you would give to minimise any problems and manage his migraines.  [50%]

(b) The codeine based painkillers Mr JZ has been using are available OTC whereas diamorphine is commonly used in palliative care painkillers. With reference to their structure, in comparison to morphine, explain why these two opioid analgesics have different activities.

(c) Naloxone can be used as a treatment for accidental overdose, whereas molecule 1 cannot. Explain with the aid of diagrams, why the Snyder theory can explain how these two molecules behave differently at opioid receptors.  [30%]
33. Answer ALL parts (a) to (e).

(a) What are first and second line therapies for acute seizure management considering both choice of seizure therapy and supportive management options? [20%]

(b) Discuss the disease, drug and patient factors involved in choice of antiepileptic therapy for long term management of epilepsy. [30%]

Clonazepam is one of the drugs used for the treatment of seizures in epilepsy.

(c) Draw the structure of the major Phase I metabolite of clonazepam. How does the metabolism affect the biological activity of the drug? [10%]

(d) The synthesis of clonazepam is achieved in three steps as shown below. Give reagents and reaction conditions for steps (i), (ii) and (iii). [25%]

(e) Clonazepam can be considered to be the chlorinated derivative of nitrazepam which is an approved drug in itself. Suggest three different properties that are beneficially altered by adding the chlorine present in clonazepam. [15%]