**Question 1**

Which of the following is TRUE regarding the pharmakokinetics of morphine?

A Morphine has a high first pass metabolism

B Enterohepatic circulation of morphine represents a large proportion of the excretory process.

C 60% bound to plasma proteins

D No amount of unchanged drug is be found in the urine

Explanation A

Morphine has a high first pass metabolism; therefore the oral dose may need to be greatly increased (as compared to the parenteral dose) to achieve a therapeutic effect. Although all opioids bind to plasma proteins with varying affinity, the drug rapidly leaves the blood compartment and localises in tissues that are highly perfused e.g. brain, liver, kidneys and spleen. Drug concentration in muscle may be much lower but this tissue still serves as the main reservoir because of its greater bulk. Metabolism is mainly in the liver (polar metabolites: glucuronides) and excretion via the kidneys. Small amount of unchanged drug may be found in the urine. In addition, glucuronide metabolites are found in bile, but enterohepatic circulation represents only a small proportion of the excretory process.

**Question 3**

Opioid metabolism includes the following

A Remifentanil is rapidly hydrolysed by common blood esterases into morphine

B There are no active metabolites of morphine

C Codeine undergoes hepatic metabolism by the P450 system

D Morphine metabolites are able to cross the blood brain barrier and do not contribute to the significant CNS effects that are seen with morphine.

Explanation C

The opioids are largely converted to polar metabolites (mostly glucuronides), which are then excreted by the kidney. 10% of morphine is metabolised to morphine 6 glucuronide, an active metabolite with 4-6x the potency of its parent compound.

Note, these metabolites are not readily able to cross the blood brain barrier and do not contribute to the significant CNS effects that are seen with morphine. Nevertheless accumulation of these metabolites can produce unwanted side effects in patients with renal failure and when large doses of morphine are given over long periods.

Heroin and remifentanil are rapidly hydrolysed by **common tissue esterases** into morphine, which has 1/4600th the potency of remifentanil

Hepatic oxidation is the prime route of degradation for the phenylpiperidine opiods (remifentanyl, fentanyl, alfentanyl, and sufentanyl). This leaves only a small amount of parent drug for renal excretion. **There are no active metabolites of fentanyl**

Codeine, oxycodone and hydrocodone undergo hepatic metabolism by the P450 system resulting in metabolites of grater potency.

**Question 7**

Regarding ketamine, which of the following statements is correct?

A It causes a brief period of increased respiratory rate

B It possesses no analgesic properties

C It is a cardiovascular stimulant via a central mechanism

D It decreases cerebral blood flow

Explanation C

Ketamine is closely related to phencyclidine. It produces a dissociative amnesic anaesthetic state characterised by: catatonia, amnesia, and analgesia without the loss of consciousness (hypnosis). It binds to the NMDA receptor. It stimulates the cardiovascular system (+inotropy) via the central sympathetic nervous system. It causes a decrease in respiratory rate but preserves respiratory reflexes and produces bronchodilation. Ketamine inhibits histamine release. CNS effects include an increase in blood flow to the brain, brain oxygen consumption and intracranial pressure. Side effects include agitation and emergence phenomenon in children.

**Question 8**

Which of the following is FALSE regarding the pharmakokinetics of morphine?

A Small amount of unchanged drug may be found in the urine

B Enterohepatic circulation of morphine represents a large proportion of the excretory process.

C Drug concentration in muscle may be much lower but this tissue still serves as the main reservoir because of its greater bulk.

D Metabolism is mainly in the liver (polar metabolites: glucuronides)

Explanation B

Morphine has a high first pass metabolism; therefore the oral dose may need to be greatly increased (as compared to the parenteral dose) to achieve a therapeutic effect. Although all opioids bind to plasma proteins with varying affinity, the drug rapidly leaves the blood compartment and localises in tissues that are highly perfused e.g. brain, liver, kidneys and spleen. Drug concentration in muscle may be much lower but this tissue still serves as the main reservoir because of its greater bulk. Metabolism is mainly in the liver (polar metabolites: glucuronides) and excretion via the kidneys. Small amount of unchanged drug may be found in the urine. In addition, glucuronide metabolites are found in bile, but enterohepatic circulation represents only a small proportion of the excretory process.

**Question 9**

Ketamine is chemically related to which of the following?

A Propofol

B Phencyclidine

C LSD

D Thiopentone

Explanation B

Ketamine is closely related to phencyclidine. It produces a dissociative amnesic anaesthetic state characterised by: catatonia, amnesia, and analgesia without the loss of consciousness (hypnosis). It binds to the NMDA receptor. It stimulates the cardiovascular system (+inotropy) via the central sympathetic nervous system. It causes a decrease in respiratory rate but preserves respiratory reflexes and produces bronchodilation.Ketamine inhibits histamine release . CNS effects include an increase in blood flow to the brain, brain oxygen consumption and intracranial pressure. Side effects include agitation and emergence phenomenon in children.

**Question 10**

A high degree of tolerance can be expected to all these effects of morphine EXCEPT?

A Miosis

B Cough supression

C Nausea

D Analgesia

Explanation A

Tolerance does not occur with miosis, constipation and convulsions

There is only a moderate degree of tolerance to bradycardia

High tolerance to analgesia, euphoria, mental clouding, sedation, respiratory depression, antidiuresis, nausea and vomiting and cough suppression

**Question 11**

Why is methadone is used in the treatment of narcotic addiction?

A It produces a short withdrawl when ceased

B It does not produce constipation

C It is a phenylpiperadine class narcotic agonist

D Tolerance and physical dependence develop more slowly with methadone

Explanation D

Methadone produces a milder but longer withdrawal when stopped than morphine. It has proven to be beneficial in treating chronic pain when morphine has failed. Pethidine is a phenylpiperadine class narcotic agonist. A side effect of methadone is constipation. Methadone is widely used in the treatment of opioid abuse. Tolerance and physical dependence develop more slowly with methadone than with morphine. The withdrawal signs and symptoms occurring after abrupt discontinuation of methadone are milder, although more prolonged, than those of morphine. These properties makes methadone useful drug for detoxification and for maintenance of chronic relapsing heroin addict.

Methadone is not a phenylpiperadine. It is a phenylheptylamine.

**Question 12**

What effects do kappa receptors mediate?

A Physical dependence

B Slows gastrointestinal transit

C Antidepressant effects

D Respiratory depression

Explanation B

Kappa receptors mediate supraspinal analgesia, spinal analgesia, psychotomimetic effects, slow gastrointestinal transit, inhibit ADH release, cause miosis, sedation and dysphoria

Mu receptors - decreases respiration, supraspinal and spinal analgesia, sedation, slow GIT transit, modulation of hormone and neurotransmitter release, causes physical dependence, miosis and euphoria,

Delta receptors - supraspinal and spinal analgesia, and modulation of hormone and neurotransmitter release

**Question 16**

Regarding dextropropoxyphene, which of the following statements is correct?

A It is structurally related to methadone

B When combined with paracetamol is a strong anti inflammatory

C Overdose causes death from hepatotoxicity

D It is a strong opiod

Explanation A (Digesic)

Dextropropoxyphene is a centrally acting, synthetic opioid analgesic structurally related to methadone. Combination with paracetaomol produces extra pain relief but no anti-inflammatory actions. The potency of the drug is about two thirds that of codeine.

Note: Overdose results in hepatoxicity (due to paracetamol) and CNS depression (due to opioid overdose). However, death due to overdose is usually because of Cardio-respiratory depression.

**Question 18**

Regarding opioid agonists and antagonists, which is incorrect?

A Naloxone is a pure antagonist

B Buprenorphine is an agonist-antagonist opioid

C Codeine is a strong opioid agonist

D Nalmefene is available only in IVI preparation

Explanation C

Codeine is a partial agonist. It is less efficacious than morphine. It can antagonize strong agonists.

Buprenorphine is a partial mu agonist and a kappa antagonist.

Naloxone and naltexone are pure antagonists.

Nalmefene, the newest of the opioid antagonists is only available in IVI preparation.

Note:

Nalmefene is available in an oral formulae 10mg, however it is not PBS listed (as of 2015) in Australia

The current textbook says that is only available as an IVI formulae. For exam purposes this would have to be true

Extra: Codeine's predominant analgesic effect comes from metabolism to morphine via CYP2D6.

**Question 19**

Regarding dextropropoxyphene, which of the following statements is false?

A It is structurally similar to methadone

B It produces greater pain relief when used with paracetamol

C It should never be used in patients with renal failure

D It has no anti-inflammatory properties

Explanation C

Dextropropoxyphene is a centrally acting, synthetic opioid analgesic structurally related to methadone. Combination with paracetaomol produces extra pain relief but no anti-inflammatory actions. The potency of the drug is about two thirds that of codeine. In patients with renal failure it should be used with caution as since higher concentration or delayed administration may occur

**Question 20**

Regarding ketamine, which of the following statements is correct?

A It has no cardiovascular effects

B It is a bronchoconstrictor

C It increases respiratory rate initially

D It can cause agitation and an emergence phenomina in children

Explanation D

Ketamine is closely related to phencyclidine. It produces a dissociative amnesic anaesthetic state characterised by: catatonia, amnesia, and analgesia without the loss of consciousness (hypnosis). It binds (inhibits) to the NMDA receptor. It stimulates the cardiovascular system (+inotropy) via the central sympathetic nervous system. It causes a decrease in respiratory rate but preserves respiratory reflexes and produces bronchodilation. Ketamine inhibits histamine release. CNS effects include an increase in blood flow to the brain, brain oxygen consumption and intracranial pressure. Side effects include agitation and emergence phenomenon in children.

Extra: Ketamine is partially water-soluble and highly lipid soluble, low protein binding 12%, metabolised in the liver to an active (although less potent metabolite-norketamine) and renally excreted. The effects of a single bolus injection is terminated by redistribution to inactive tissue sites

**Question 21**

Regarding Methadone, which of the following is true?

A Half life of methadone 12-24hrs

B It has a lower bioavailability than morphine

C It binds to opioid and non opioid receptors

D Withdrawal symptoms are less prolonged than with morphine

Explanation C

Methadone is well absorbed from the GIT tract. Its bioavailability far exceeds that of morphine. It is an agonist at the mu receptors and an antagonist at the non opioid receptors including NMDA and monoaminergic reuptake receptors. These receptor properties may explain methadone's ability to treat chronic pain and cancer patients when regular opioids have failed. It has a long half life of 25-52hrs.

Tolerance and physical dependence develop more slowly with methadone than with morphine. Withdrawal symptoms following an abrupt stopping of methadone produce milder but more prolonged symptoms than morphine withdrawal. Theses properties make methadone a useful drug for detoxification and for maintenance for the chronic relapsing heroin addict.

For detoxification of a heroin addict, methadone (5-10mg) is given 2-3 times daily for 3 days. Upon discontinuing methadone, the patients experiences a mild but endurable withdrawal syndrome.

**Question 22**

To which of the following does opioid tolerance not occur?

A Miotic effect

B Cough suppression effect

C Hypotensive effect

D Respiratory depression effect

Explanation A

Opioid tolerance developes to the analgesic, sedating and respiratory depressant effects. Tolerance also develops to the antidiuretic, emetic, cough suppression and hypotensive effects but not to the miotic, convulsant and constipating actions

Opioids when used chronically, the patient will develop tolerance to its effects. Tolerance will develop to the physiological effects of opioids and euphoric, analgesic effects. However, no matter how often/long you use opioids or how high the dose is, you will not get a physiological tolerance to miosis of the pupil, you will still get constipated and you can still convulse. Your body cannot over come these side effects (cannot build a tolerance to them)

**Question 24**

Regarding naloxone, which of the following statements is correct?

A It has a half life of between 1 and 2 hours

B It has a half life of less than one hour

C It has a half life of between 2 and 3 hours

D It has a half life of between 3 and 4 hours

Explanation A

Naloxone has a duration of action of 1-2 hours when given by injection and 10 hours when taken via the oral route. Although naloxone is well absorbed via the oral route it undergoes rapid first pass metabolism. There is no tolerance to the antagonistic action of these agents, nor does withdrawal after chronic administration precipitate an abstinence syndrome.

MIMS reports the half-life of Naloxone to be about 60min in adults with a range of 30-80 minutes, and about 3hrs in neonates

The current TB states that Naltrexone has a half-life of 10hrs. The elimination half-life is 60-90min

**Question 25**

Which opioid analgesic has the longest duration of analgesia?

A Buprenorphine

B Morphine

C Codeine

D Methadone

Explanation A

Morphine= 4-5hrs

Codeine= 3-4hrs

Buprenorphine= 4-8hrs

Methadone= 4-6hrs

**Question 26**

Which is true regarding common opioid analgesics?

A Sufentanil can be given orally and intravenously

B Alfentanil has the shortest duration of analgesia

C Morphine has analgesic effects on mu, kappa and delta receptors

D Codeine is a partial mu receptor agonist

Explanation D

Morphine has analgesic effects on the mu receptor. Although it is an agonist to kappa and delta receptors as well, there is doubt as to the actual analgesic action it produces at these receptor sites. Morphine has analgesia duration of 4-5hrs. Codeine is a partial mu receptor agonist. Sufentanil is a mu, kappa and delta receptor agonist. Methadone is a mu receptor agonist. Sufentanil can only be given parenterally. Remifentanil has the shortest duration of analgesia-0.05hrs. Buprenorphine has the longest duration of analgesia-4-8hrs. Alfentanil has analgesia duration of 0.25-0.75hrs.

**Question 27**

Which of the following opioids have INACTIVE metabolites?

A Methadone

B Oxycodone

C Morphine

D Codeine

Explanation A

Morphine=hydromorphone.

Codeine= morphine

Oxycodone= oxymorphone.

Pethidine = norpethidine

Unlike codeine, morphine, hydromorphone, pethidine or oxycodone, methadone has no active metabolites and is therefore a good choice for patients at risk for toxicity from metabolite accumulation

**Question 28**

Which of the following statements regarding Naloxone is false?

A Intravenous administration reverses opioid effects in 1-2min

B Naloxone has equal affinity for mu, kappa and delta receptors

C Tolerance to naloxone does not develop

D Naloxone is a pure antagonist

Explanation B

Naloxone is a pure antagonist. It has a very high affinity for mu receptors and a lower affinity for the other receptor binding sites. Naloxone has a half life of 1-2 hours when given by injection and 10 hours when taking via the oral route. Although naloxone is well absorbed via the oral route it undergoes rapid first pass metabolism. IVI administration reverses opioid toxicity in 1-3 minutes. There is no tolerance to the antagonistic action of these agnets, nor does withdrawal of naloxone after chronic administration precipitate an abstinence syndrome