

13. Imagine a drug that is eliminated entirely by glomerular filtration, but 50% of the filtered drug is reabsorbed back in the proximal tubule and returns to the systemic circulation. The other 50% of the filtered drug is excreted into the urine. In a person with a glomerular filtration rate of 100 mL/min (same as 6 L/hr), calculate the expected drug clearance. You can assume that 100% of the drug is free in circulation (i.e., do not be concerned about protein-bound versus free drug).

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- (B) 3 L/hr
- (C) 6 L/hr
- (D) 9 L/hr
- (E) 12 L/hr

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14. In an attempt to commit suicide, a 90 kg institutionalized patient is believed to have taken a “handful” of (immediate-release) lithium tablets stolen from an accidentally unlocked medicine cabinet. These tablets are rapidly absorbed and 100% orally bioavailable, with peak levels seen within 0.5 hrs for normal therapeutic doses and up to 2 hrs maximum in overdose. The patient is carefully observed and blood samples are drawn serially, approximately every 30 minutes, for the next three hrs. The levels demonstrate a rapid rise over the first hour to a peak level of 1.0 mmol/L, followed by a slow, exponential decline over the next two hrs. Lithium has a very predictable volume of distribution of 0.3 L/kg and is eliminated by renal excretion with a half-life of 18 to 24 hrs. An audit of the medicine cabinet reveals that twenty 300 mg lithium tablets are missing. Which of the following statements regarding the potential use of the patient’s peak level to estimate the number of tablets consumed is correct? You can assume that each 300 mg tablet of lithium carbonate contains about 4 mmol of lithium.

(A) it is not appropriate to use the peak level to estimate dosage because a majority of the lithium is likely to have been eliminated during the absorption phase

(B) it appears that about two-thirds of the stolen lithium tablets are still missing

(C) the patient’s peak level is consistent with complete absorption of all twenty 300 mg lithium tablets

(D) use of the peak level is invalid, because the patient was likely still absorbing when the 1.0 mmol/L level was taken

(E) use of the peak level is invalid, because a majority of the lithium was likely eliminated by first-pass hepatic metabolism

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15. Maintaining a therapeutic drug level (i.e. drug concentration within the therapeutic range) throughout an intermittent dosing interval can be challenging. Important factors to consider are the drug's half-life, rate of absorption, therapeutic index, and dosing schedule. For a patient experiencing a loss of drug efficacy shortly before their once daily dosage (when their drug level is at its lowest), which of the following statements regarding dosage adjustments is most appropriate.

(A) a simple increase in the daily dosage may be sufficient, as long as signs of drug toxicity are carefully monitored in the time period immediately following each daily dose

(B) prescription of a second medication that will induce metabolism of the first will be effective in this scenario

(C) taking half as much medicine twice per day (same amount total) instead of the same total once per day is NOT likely to help

(D) taking the medication on an empty stomach to increase the rate of absorption (but not the bioavailability) is likely to help

(E) an extended release formulation of the same drug is NOT likely to help

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16. Which of the following statements regarding the effect of drug metabolizing reactions is **NOT** correct?

- (A) conjugation of drugs to highly polar molecules generally increases the water solubility of drugs
- (B) some drugs are inactive until enzymatic modification in the body, often referred to as pro-drugs
- (C) increased water solubility of drug metabolites enhances renal excretion
- (D) drug oxidation catalyzed by phase I enzymes often reduces drug affinity for tissue-binding sites
- (E) hepatic drug metabolism generally enhances oral bioavailability

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17. Which of the following is **NOT** a characteristic of Phase I drug metabolizing reactions?

- (A) genetic polymorphism is high in the human population
- (B) malnourishment preferentially decreases the efficacy of Phase I reactions with little effect on Phase II reactions
- (C) they involve the addition of small functional groups to create a more polar compound
- (D) chronic alcohol consumption results in a net increase in their activity (i.e. induction)
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18. Which of the following statements regarding inter-individual variability in drug metabolism is **NOT** correct?

- (A) long term pharmacotherapy with phenytoin will net induce (increase) P450 metabolism
- (B) glucuronidation of drugs is often decreased in infants
- (C) phase I drug metabolism is generally reduced in the elderly more than phase II reactions
- (D) drug metabolism is significantly affected by early stage liver disease
- (E) catabolic syndromes such as “cancer cachexia” hinder drug metabolism reactions similar to chronic food deprivation (malnourishment)

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19. A patient presents to the emergency department approximately 12 hrs following the acute ingestion of an unknown number of acetaminophen tablets. An initial acetaminophen level was 100 ng/mL, followed by a level of 50 ng/mL 4 hrs later, and 25 ng/mL 4 hrs after that (or 8 hrs since the first level). Which one of following statements is correct?

(A) because the fraction eliminated in the first 4 hrs is the same as the fraction eliminated in the second 4 hrs, this patient is eliminating acetaminophen by zero-order (aka non-linear or saturating) pharmacokinetics

(B) acetaminophen is being eliminated with an 8 hr half-life in this patient and is consistent with acetaminophen toxicity

(C) acetaminophen is being eliminated with a 4 hr half-life in this patient and is consistent with acetaminophen toxicity

(D) this patient is not likely to experience hepatotoxicity from the acetaminophen ingestion because the critical value of 150 ng/mL was not obtained

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20. Codeine (an opiate analgesic) is metabolized by two P450 enzymes. In a therapeutic dose, 80% of the administered codeine is converted into norcodeine by the enzyme CYP3A4 and 20% is converted into morphine by the enzyme CYP2D6. Morphine is responsible for a majority of the therapeutic and potentially toxic effects of codeine, as it has much better CNS penetration than either codeine or norcodeine. CYP2D6 is genetic polymorphic in humans. CYP3A4 is often selectively inhibited or induced by specific drugs. These factors must be considered when prescribing codeine. Which of the following statements is **NOT** correct (or, alternatively, do you believe that all the statements are correct)?

- (A) codeine dosage may need to be lowered in patients taking the HIV protease inhibitor combination liponavir/ritonavir, which powerfully inhibits CYP3A4 activity but also induces the activity of the remaining P450 enzymes
- (B) patients who have one deficient CYP2D6 allele and one normal allele (overall lowered activity) may require higher doses of codeine for the same therapeutic effect
- (C) patients with gene duplication of CYP2D6 and therefore ultra-high enzyme levels (known as ultra-rapid metabolizers) and are also on partial inhibitors of the CYP3A4 enzyme may become toxic on typical, therapeutic dosages of codeine
- (D) patients who are homozygous for inactive CYP2D6 alleles are at increased risk for toxicity from codeine
- (E) all of the above are correct

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21. Oxycodone is a powerful analgesic (pain reliever). It is metabolized in the liver by a cytochrome P450 enzyme to oxymorphone. Both oxycodone and oxymorphone are conjugated with glucuronic acid, at the same rate, and the conjugated molecules are effectively cleared renally. Both of the unconjugated forms of oxycodone and oxymorphone are **equally** effective pain relievers, but their glucuronidated forms have **NO** physiologic effect. Which of the following clinical scenarios (if any) is likely to require an increase in oxycodone dosage to maintain the same steady-state level of the active compounds (i.e., the sum of unconjugated oxycodone and unconjugated oxymorphone)?

- (A) a malnourished cancer patient
- (B) someone who has been taking phenobarbital chronically
- (C) someone who takes cimetidine for heartburn multiple times daily
- (D) someone with around 50% of the normal glomerular filtration rate due to kidney disease
- (E) an increase in dosage is not indicated in any of the above scenarios

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