

## Pharm General Principles

### Questions 1-10: Dickchenamine

500 mg of dickchenamine is administered rectally to a 70 kg “volunteer” in a secret CIA prison in eastern Europe. Because of “treatment” not entirely endorsed by the Geneva Convention, the “volunteer” has a GFR of 20 ml/min.

Known facts about dickchenamine:

- half life = 4 hours
- volume of distribution = 9.11 L/kg.
- extraction ratio = 0.4
- oral availability = 80%
- rectal availability = 90%
- target concentration = 10 mg/L

1. What is the clearance of dickchenamine?

- A) 0.79 L/h/70kg
- B) 1.58 L/h/70kg
- C) 2.28 L/h/70kg
- D) 3.16 L/h/70kg
- E) 6.32 L/h/70kg

2. What is the rate of elimination of dickchenamine, assuming 500 mg were administered IV?

- A) 43.4 mg/L
- B) 54.9 mg/L
- C) 86.7 mg/L
- D) 130 mg/L

3. What is the systemic availability of dickchenamine delivered rectally?

- A) 32%
- B) 40%
- C) 48%
- D) 60%
- E) 80%
- F) 90%
- G) 100%

4. What is the systemic availability of dickchenamine delivered orally?

- A) 32%
- B) 40%
- C) 48%
- D) 60%
- E) 80%
- F) 90%
- G) 100%

5. If the volume of distribution of dickchenamine were 100 times higher, what would that tell you?

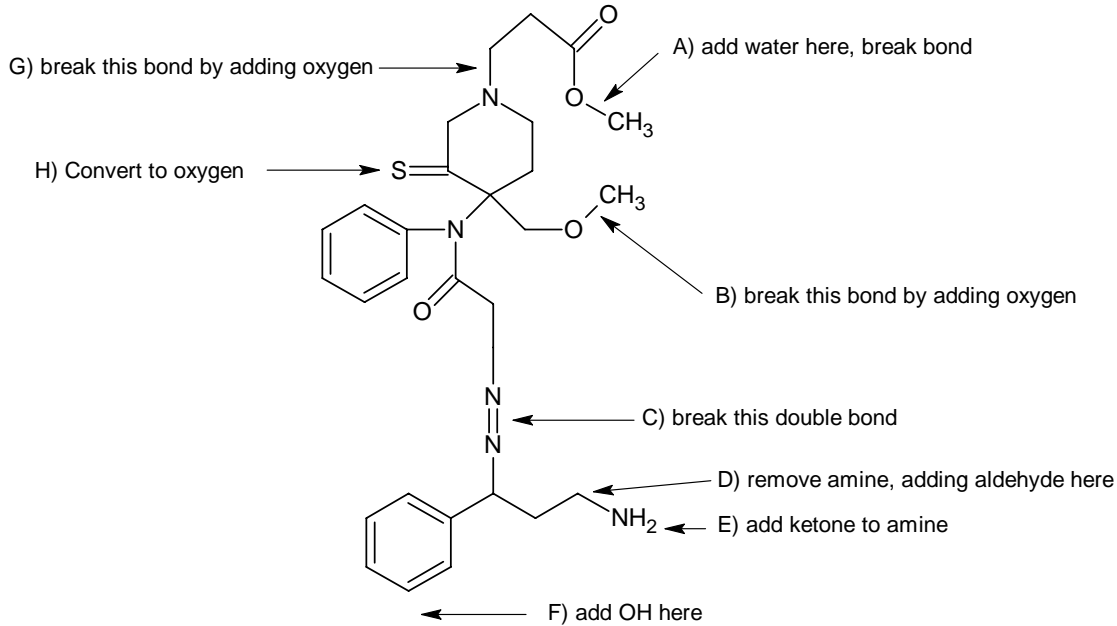
- A) the drug is cleared relatively quickly
- B) the drug is cleared relatively slowly
- C) the drug remains mostly in the plasma
- D) the drug remains mostly in the ICF
- E) the drug raises venous capacitance

6. What average rectal dosing rate is necessary to achieve the target concentration, assuming the “volunteer” had a normal GFR?

- A) 1.76 mg/h/70kg
- B) 1.98 mg/h/70kg
- C) 17.6 mg/h/70kg
- D) 19.8 mg/h/70kg

7. What would the approximate average maintenance dose be if dickchenamine were administered orally twice a day, assuming a normal GFR?
- A) 7.9 mg
  - B) 15.8 mg
  - C) 158 mg
  - D) 395 mg
  - E) 474 mg
8. What oral loading dose should be given to quickly raise the serum level of dickchenamine to the target concentration, assuming a normal GFR?
- A) 9.11 mg
  - B) 57 mg
  - C) 190 mg
  - D) 237 mg
  - E) 474 mg
9. What is the actual corrected maintenance dose for the "volunteer" given his reduced GFR, assuming that renal excretion accounts for 100% of the drugs metabolism?
- A) 7.9 mg
  - B) 15.8 mg
  - C) 79 mg
  - D) 158 mg
  - E) 237 mg
10. A second drug was given, valplamenol, that increases the clearance of dickchenamine twofold. How long would it take for dickchenamine to be entirely cleared (assume normal GFR)?
- A) 8 hours
  - B) 16 hours
  - C) 24 hours
  - D) 32 hours
  - E) 64 hours
11. In a comparison of drug-receptor binding and dose-response curves, how do you interpret an experiment where  $EC_{50} < K_d$ ?
- A) The experiment was conducted in the presence of a competitive agonist
  - B) Such a system will show increased sensitivity to the drug compared to a system where  $EC_{50} = K_d$
  - C) The spare receptors in the system have been bound by a noncompetitive antagonist
  - D) Such a result is impossible
12. If drug A is more potent than drug B, then which statement is true?
- A) A has a higher maximal effect than B
  - B) A and B cannot be equally effective
  - C) It takes less of A to get the same effect as the same amount of B
  - D) A dose-response graph of A and B will show B's curve looking like a partial agonist compared to A
13. A dose response curve is plotted of a full agonist. As increasing concentrations of a partial agonist are added to the experiment, the resulting response curve initially looks like that of:
- A) noncompetitive inhibitor
  - B) competitive inhibitor
  - C) physiological antagonist
  - D) the curve would be unchanged
  - E) the curve would be increased in maximal effect

Questions 14-21: Drug metabolism Mix and Match



14. The reaction is catalyzed by P450 and involves an unstable epoxide intermediate
15. N-dealkylation (P450)
16. O-dealkylation (P450)
17. Desulfuration (P450)
18. Most likely to occur in gut catalyzed by bacterial enzymes
19. Can occur in many tissues in the body
20. Catalyzed by monoamine oxidase
21. A mutation in the enzyme that catalyzes this reaction is autosomal dominant and common in Asians.

Clinical Drug Development: Mix and Match, may be used more than once or not at all

- A) Phase I Clinical Trial
  - B) Phase II Clinical Trial
  - C) Phase III Clinical Trial
  - D) Phase IV Clinical Trial
22. After this phase, the drug company may apply for marketing approval
  23. This phase focuses on adverse effects in specific subpopulations of patients
  24. This phase involves studies in a large number of patients to evaluate efficacy and adverse-effect profile.
  25. This phase is primarily concerned with safety and tolerability in normal volunteers

**Answers:**

1. **B:** Clearance can be calculated from the formula for half life:  $t_{1/2} = \frac{0.693 * V_d}{CL} = \frac{0.693 * 9.11}{CL} = 4$

Clearance comes out to be 1.58 L/h/70kg.

2. **C:** rate of elimination = CL \* C

We don't know C, but we can calculate it from the formula for volume of distribution:

$$V_d = \frac{\text{amount of drug}}{C} = \frac{500 \text{ mg}}{C} = 9.11 \rightarrow C \text{ comes out to be } 54.9 \text{ mg/L}$$

When we plug C=54.9 mg/L into the formula for rate of elimination, we get RE = 86.7 mg/h/70kg.

3. **F:** Rectally administered drugs do not pass through the liver, so the systemic availability is the same as the rectal availability, which is 90%.

4. **C:** Orally administered drugs do pass through the liver, so systemic availability = f(1-ER)

5. **D:** High volume of distribution (much higher than plasma volume) implies that the drug crosses into the extravascular compartment.

6. **C:**  $DR_{(rectal)} = \frac{CL * TC}{f_{(rectal)}} = \frac{1.58 * 10}{0.9}$

Just plugging in the numbers, dosing rate comes to 17.6 mg/h/70kg. You first need to calculate the clearance (question #1).

7. **D:** Maintenance dose =  $\frac{DR * DI}{f(1-ER)}$

The DR (dosing rate) is CL \* TC = (1.58 L/h/70kg) \* (10 mg/L) = 15.8 mg/h/70kg.

DI is the dosing interval, in hours. In this case, twice a day implies a DI of 12 hours. Oral availability (f) is 0.8. Systemic availability is f(1-ER) = 0.48. Therefore, the maintenance dose is 395 mg every 12 hours.

8. **C:** Loading dose =  $\frac{V_d * TC}{f(1-ER)} = \frac{9.11 * 10}{0.8(1-0.4)}$

So he should take about 189.8 mg of loading dose. Note that giving a loading dose for this drug doesn't make a whole lot of sense, because it has a pretty short half life and therefore doesn't take a lot of time to accumulate. The loading dose is actually less than the maintenance dose. The only point of this is to use the silly formula for loading dose.

9. **C:** His GFR is 20% of normal (a GFR of 100 ml/min is considered normal). Therefore, he should get 20% of whatever maintenance dose would be calculated for a normal person. (the answer was changed to reflect the corrected MD)

10. **A:** According to the formula for half life, doubling the clearance would half the half life:

$$t_{1/2} = \frac{0.693 * V_d}{CL}$$

Since the original half life was 4 hours, the half life is 2 hours with valplamenol. By convention, it takes 4 half lives for a drug to be "completely cleared." (even though in reality it's not 100% cleared after 4 half lives).

11. **B:** Kd is the concentration of drug where half the receptors are bound. EC50 is the concentration of drug required for 50% of maximum effect that the drug is capable of. If EC50 is less than Kd, that implies that you don't need to bind 50% of the receptors to get 50% of the response. Therefore, such a system would be more sensitive than a system where you do have to bind 50% of the receptors to get 50% of the full response.

12. **C**

13. **A**

14. **F:** aromatic hydroxylation

15. **G**

16. **B**

17. **H**

18. **C:** Azo reduction

19. **A:** Catalyzed by Esterase

20. **D**

21. **E:** Acetyl transferase

22. **C**

23. **D**

24. **C**

25. **A**