

PHA 5127 Case Study 5 2013

1. A male patient (30-year old, 100kg, 5'5" height) was given a 400 mg IV bolus dose of drug X. His serum creatinine level was determined to be 1.0 mg/dL.

a) Please calculate the patient's creatinine clearance.

$$\begin{aligned} \text{IBW}_{\text{male}} &= 50\text{kg} + 2.3 \text{ kg for each inch over 5 ft in height} \\ &= 50 \text{ kg} + 2.3 \text{ kg} \times 5 \\ &= 61.5 \text{ kg} \end{aligned}$$

$$\text{TBW} = 100 \text{ kg} > \text{IBW} \times 120\% = 73.8 \text{ kg}$$

Based on his TBW and height, the patient is considered obese. As a result, ABW needs to be used for the computation of creatinine clearance, which is computed as follows:

$$\text{ABW} = \text{IBW} + 0.4 (\text{TBW} - \text{IBW}) = 61.5 \text{ kg} + 0.4 \times (100 \text{ kg} - 61.5 \text{ kg}) = 76.9 \text{ kg}$$

$$\text{CrCl}_{\text{male}} = \frac{(140 - \text{age}) \times \text{ABW}}{72 \times \text{SerumCreatinine}} = \frac{(140 - 30) \times 76.9 \text{ kg}}{72 \times 1.0 \text{ mg/dL}} = 117 \text{ mL/min}$$

b) Assume that drug X is solely eliminated via the kidneys. The volume of distribution of drug X is 20 L. Please calculate the half-life, $\text{AUC}_{0 \sim \infty}$, and plasma concentration after 8 hours of drug X.

$$\text{CL}_{\text{total}} = \text{CrCl} = 117 \text{ mL/min} = 117 \times \frac{1000 \text{ L}}{60 \text{ h}} = 7 \text{ L/h}$$

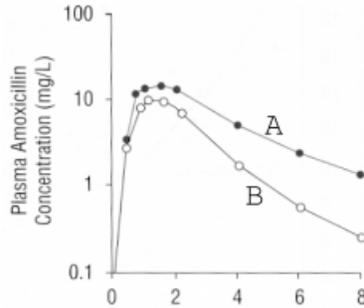
$$k_e = \frac{\text{CL}}{V_d} = \frac{7 \text{ L/h}}{20 \text{ L}} = 0.35/\text{h}$$

$$t_{1/2} = \frac{0.693}{k_e} = \frac{0.693}{0.35/\text{h}} = 1.98 \text{ h}$$

$$\text{AUC}_{0 \sim \infty} = \frac{\text{Dose}}{\text{CL}} = \frac{400 \text{ mg}}{7 \text{ L/h}} = 57.1 \text{ mg} \cdot \text{h/L}$$

$$C_t = \frac{\text{Dose}}{V_d} e^{-k_e \times t} = \frac{400 \text{ mg}}{20 \text{ L}} e^{-0.35/\text{h} \times 8 \text{ h}} = 1.21 \text{ mg/L}$$

2. The image below shows an Amoxicillin concentration-time profile when administered with and without Probenecid. Amoxicillin is eliminated solely via the kidneys and Probenecid inhibits its active renal secretion. Please identify the curve that corresponds best to Amoxicillin when administered alone or in combination with Probenecid. Justify your answer by comparing the PK parameters, such as the peak plasma concentration (C_{max}), half-life ($t_{1/2}$), renal clearance (CL_R), total clearance, etc. between the two scenarios.



Answer: Open circle (curve B) is the plasma concentration-time profile of Amoxicillin when administered only, close circle (curve A) is the plasma concentration-time profile of Amoxicillin when administered with Probenecid.

From the image, we can see $C_{max} A > C_{max} B$

$$CL A < CL B$$

$$t_{1/2} A > t_{1/2} B$$

$$AUC_{0 \sim \infty} A > AUC_{0 \sim \infty} B$$

Because Probenecid inhibits renal active secretion, which

$$CL \approx CL_R = CL_{\text{renal filtration}} + CL_{\text{renal secretion}} - "CL"_{\text{reabsorption}}$$

When renal active secretion is decreased, renal clearance is decreased. Then total clearance is decreased, C_{max} is increased, and drug exposure is increased.

3. Based on the information given below, state the likely involvement of filtration, secretion, and tubular reabsorption in the renal clearance (CL_R) of each drug listed. The GFR (glomerular filtration rate) is 120 mL/min and urine flow is 1.5 mL/min.

	CL_R (mL/min)	Fraction unbound in plasma (f_{up})
Theophylline	10	0.50
Phenytoin	0.15	0.10
Cefonicid	20	0.02
Digoxin	100	0.79

Theophylline:

$$CL_{\text{filtration}} = f_{up} \times GFR = 0.50 \times 120 \text{ mL/min} = 60.0 \text{ mL/min} > CL_R = 10 \text{ mL/min};$$

Filtered and reabsorbed

Phenytoin:

$$CL_{\text{filtration}} = f_{up} \times GFR = 0.10 \times 120 \text{ mL/min} = 12.0 \text{ mL/min} > CL_R = 0.15 \text{ mL/min};$$

Filtered and extensively reabsorbed

Cefonicid:

$$CL_{\text{filtration}} = f_{\text{up}} \times \text{GFR} = 0.02 \times 120 \text{ mL/min} = 2.4 \text{ mL/min} < CL_R = 20 \text{ mL/min};$$

Filtered and secreted

Digoxin:

$$CL_{\text{filtration}} = f_{\text{up}} \times \text{GFR} = 0.79 \times 120 \text{ mL/min} = 94.8 \text{ mL/min} \approx CL_R = 100 \text{ mL/min};$$

Either filtered and neither secreted nor reabsorbed, or that secretion and reabsorption occurs but occur to an approximately equal extent.

4. The renal clearance of inulin is equal to the GFR. Which statement is incorrect regarding inulin?

- (A) It is not bound to plasma proteins
- (B) It undergoes renal tubular secretion
- (C) It does not undergo passive reabsorption
- (D) It does not undergo active reabsorption
- (E) Both A and D

Answer: (A) is true, (B) is false, (C) is true, (D) is true, (E) is true. So B is the final answer.