

**Case Study # 3**  
**Answers Provided by**  
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- 1) Mr. I. P. Freely is a 5'6'' 40 y.o. man has a serum creatinine level of 1.3mg/100mL. His best friend Inita P., a 5'2'' 20 y.o. female, has a serum creatinine level of 1.5 mg/100mL. Determine the creatinine clearance for each and compare these to the normal value. What may be deduced about the GFR of each of these individuals? Why is IBW used instead of total body weight (TBW)? IF TBW were used rather than IBW, would the  $Cl_{creat}$  be under- or over-estimated?

Given: 5'6" 40 y.o. male      5'2" 20 y.o. female  
 $Cp_{creat} = 1.3 \text{ mg/100 ml}$        $Cp_{creat} = 1.5 \text{ mg/100 ml}$

$$Cl_{creat}(\text{male}) = \frac{(140 - \text{age}) \cdot IBW}{72 \cdot Cp_{creat}} ; IBW(\text{male}) = 50\text{kg} + 2.4 \text{ kg for every inch over 5 ft.}$$

For the male patient above, the ideal body weight is

$$IBW = 50 \text{ kg} + (2.4 \text{ kg})(6) \\ = 64.4 \text{ kg}$$

The creatinine clearance is then

$$Cl_{creat}(\text{male}) = \frac{(140 - 40)(64.4)}{(72)(1.3)} = 68.8 \text{ ml / min}$$

The equations for female patients are:

$$Cl_{creat}(\text{female}) = \frac{(140 - \text{age}) \cdot IBW}{85 \cdot Cp_{creat}} ; IBW_{\text{female}} = 45.5 \text{ kg} + 2.3 \text{ kg for every inch over 5}$$

ft.

$$IBW = 45.5 \text{ kg} + (2.3 \text{ kg})(2) = 50.1 \text{ kg}$$

The creatine clearance is then

$$Cl_{creat}(\text{female}) = \frac{(140 - 20)(50.1)}{(85)(1.5)} = 47.1 \text{ ml / min}$$

The  $Cl_{creat}$  for the male patient is roughly half the normal value of 125 ml/min. That for the female patient is even lower.

Creatine is eliminated from the body via glomerular filtration and shows no protein binding. Thus, calculating  $Cl_{\text{creat}}$  is a means of obtaining the glomerular filtration rate (GFR). Since the  $Cl_{\text{creat}}$  was so low for these patients, it may be deduced that there is some kidney failure.

Since creatinine is produced by muscle metabolism, we use the IBW in calculating  $Cl_{\text{creat}}$  instead of total body weight. If total body weight were used, the clearance would be overestimated. Since we are using  $Cl_{\text{creat}}$  to estimate GFR, we would overestimate as well. This could lead to overdosing for a drug that is eliminated primarily via excretion, since we are relying on a calculated GFR which may be larger than the actual rate, i.e. less drug is being cleared from the body than we believe.

- 2) Mr. Freely's second best friend Anita Hug is hospitalized with a severe infection after being hit by a truck as she tried to write "wash me" in the dust on the truck's rear window. She is being treated with aminoglycosides. The desired peak level for the initial dose is 6 mg/L. Assuming a  $V_d$  of 0.24 L/kg (IBW), the same body weight and creatinine clearance as MR. I. P. Freely, determine the appropriate dose. For additional doses, how should this amount be modified (no calculation, just discuss).

Aminoglycoside treatment;  $V_d = 0.24 \text{ L/kg (IBW)}$

desired  $C_p = 6 \text{ mg/L}$

To determine the correct dose, we may use

$$C_{p_0} = \frac{Dose}{V_d}$$

Solving this equation for dose gives

$$D = C_{p_0} \cdot V_d$$

$C_{p_0}$  is the desired peak level and the  $V_d$  for this patient is

$$V_d = \frac{0.24L}{kg} \times 64.4kg = 15.5L$$

this dose is then

$$D = (6\text{mg/L})(15.5 \text{ L}) = \boxed{93 \text{ mg}}$$

Aminoglycosides are excreted unchanged by renal glomerular filtration. Since the GFR for this patient is lower than normal, we know that the drug is not being eliminated from the body at a usual rate. Thus, we must decrease the dose to avoid overdosing if multiple doses are given.

- 3) Theophylline is metabolized in the liver by P-450. If a patient is being treated with both theophylline and cimetidine (a known inhibitor of P-450), how should a dosing regimen of theophylline be modified? Theophylline is a low extraction drug with low protein binding.

Inhibition of P-450, the enzyme responsible for the metabolism of theophylline, would result in a decreased hepatic clearance for this drug. The general equation for hepatic clearance is

$$Cl_H = E_H \cdot Q_H,$$

Where  $E_H$  is the extraction ratio and  $Q_H$  is liver blood flow.

$$E_H = \frac{Cl_{int} \cdot fub}{Q_H + Cl_{int} \cdot fub}$$

The inhibition of P-450 causes a low intrinsic clearance,  $Cl_{int}$ . To determine the extent to which this lowers the clearance of theophylline, we need to know whether theophylline is a high-or low-extraction drug. Theophylline is a low extraction drug. Thus,

$$E_H = \frac{Cl_{int} \cdot fu}{Q_H + Cl_{int} \cdot fu} \approx \frac{Cl_{int} \cdot fu}{Q_H}$$

and then

$$Cl_H = E_H \cdot Q_H = \frac{Cl_{int} \cdot fu}{Q_H} \cdot Q_H = Cl_{int} \cdot fu$$

So, lowering  $Cl_{int}$  decreases  $Cl_H$  proportionally. Since less drug is cleared, less drug should be given in chronic treatment. This is especially important for drugs with narrow therapeutic windows.

- 4) How does an increase in hepatic blood flow affect the oral bioavailability of a high extraction drug? Are low extraction drugs affected in the same way? Explain.

Oral bioavailability ( $F_H$  - the bioavailability dependent of first pass metabolism in the liver) is given by:

$$F_H = 1 - E_H$$
$$= \frac{Q_H}{Q_H + Cl_{int} \cdot fu}$$

For a high extraction drug  $Cl_{int} \cdot fu \gg Q_H$ . Thus,

$$F_H = \frac{Q_H}{Q_H + Cl_{int} \cdot fu} \approx \frac{Q_H}{Cl_{int} \cdot fu}$$

Increasing  $Q_H$  causes an increase in bioavailability. For a low extraction drug,  $Cl_{int} \cdot fu \ll Q_H$ .

Then,

$$F_H \approx \frac{Q_H}{Q_H} = 1$$

Oral bioavailability for a low extraction drug is not dependent on liver blood flow.

Note: In working these problems it is important to use the correct equation for  $F_H$ . Using only  $F_H = 1 - E_H$  and putting in the approximation for  $E_H$  results in a gross over simplification and will give misleading answers.