Problem 1

For the following situations, indicate whether the drug is: filtered, reabsorbed (if fully or if reabsorbed through transporters), or actively secrete. Assume that the GFR is 130mL/min and that the urine flow is 1.5mL/min.

1. Drug with $f_u=0.3$ and a $Cl_{\text{ren}}=39$ mL/min
   
   $f_u \times GFR = 0.3 \times 130$ mL/min = 39 mL/min
   
   $Cl_{\text{ren}} = f_u \times GFR \rightarrow$ filtered

2. Drug with $f_u=0.6$ and a $Cl_{\text{ren}}=30$ mL/min
   
   $f_u \times GFR = 0.6 \times 130$ mL/min = 78 mL/min
   
   $Cl_{\text{ren}} < f_u \times GFR \rightarrow$ reabsorbed
   
   $f_u \times \text{urine flow} = 0.6 \times 1.5$ mL/min = 0.9 mL/min
   
   ($Cl_{\text{ren}} > f_u \times \text{urine flow}$) $\rightarrow$ not fully reabsorbed

3. Drug with $f_u=0.05$ and a $Cl_{\text{ren}}=15$ mL/min
   
   $f_u \times GFR = 0.05 \times 130$ mL/min = 6.5 mL/min
   
   $Cl_{\text{ren}} > f_u \times GFR \rightarrow$ actively secreted

4. Drug with $f_u=0.2$ and a $Cl_{\text{ren}}=0.3$ mL/min
   
   $f_u \times GFR = 0.2 \times 130$ mL/min = 26 mL/min
   
   $Cl_{\text{ren}} < f_u \times GFR \rightarrow$ reabsorbed
   
   $f_u \times \text{urine flow} = 0.2 \times 1.5$ mL/min = 0.3 mL/min
   
   $Cl_{\text{ren}} = f_u \times \text{urine flow} \rightarrow$ fully reabsorbed

5. Drug with $f_u=0.8$ and a $Cl_{\text{ren}}=0.3$ mL/min
   
   $f_u \times GFR = 0.8 \times 130$ mL/min = 104 mL/min
   
   $Cl_{\text{ren}} < f_u \times GFR \rightarrow$ reabsorbed
   
   $f_u \times \text{urine flow} = 0.8 \times 1.5$ mL/min = 1.2 mL/min
   
   $Cl_{\text{ren}} < f_u \times \text{urine flow} \rightarrow$ reabsorbed through transporters
Problem 2

T.T. (male, 6’3” tall, 111 kg, 24 years old) shows a serum creatinine level of 1.3 mg/dL.

a) Use the Cockcroft-Gault-Equation to calculate his creatinine clearance and glomerular filtration rate (GFR). Comment on the renal function of T.T.?

\[ IBW_{male} = 50kg + 2.3kg \times 15 = 84.5kg \]

\[ TBW = 111kg > IBW \times 120\% = 84.5kg \times 120\% = 101.4kg \]

Thus, use ABW is Cockcroft-Gault-Equation.

\[ ABW = IBW + 0.4 \times (TBW - IBW) = 84.5kg + 0.4 \times (111kg - 84.5kg) = 95.1kg \]

\[
CrCL_{male,obese} = \frac{(140 - a ge) \times ABW}{72 \times [Creatinine (Serum)]} = \]

\[
\frac{(140 - 24) \times 95.1kg}{72 \times [1.3 \frac{mg}{dL}]} = 117.9 \frac{ml}{min} = GFR
\]

The calculated (observed) GFR is close to the maximum GFR of 130 ml/min. Thus, the renal function of T.T. seems to be normal.

b) Why do we use the creatinine clearance to estimate the GFR?

- Creatinine is mainly eliminated by renal processes
- Creatinine is cleared by glomerular filtration only
  - No active tubular secretion
  - No tubular reabsorption
- No plasma protein binding

c) Drug A shows a plasma protein binding and tissue protein binding of 10% and 95%, respectively. Drug A is eliminated by hepatic (80%) and renal processes (20%). Calculate the total systemic clearance of drug A (in L/h) when administered to T.T. Assume that the drug is neither actively secreted nor reabsorbed.

\[ CL_{ren} = f_u \times GFR = 0.9 \times 117.9 \frac{ml}{min} = 106.1 \frac{ml}{min} = 6.36 \frac{L}{h} \]

\[ CL_{Total} = CL_{ren} + CL_{hep} = 6.36 \frac{L}{h} + CL_{hep} = 6.36 \frac{L}{h} + 0.8 \times CL_{Total} = \]

\[ CL_{Total}(1 - 0.8) = 6.36 \frac{L}{h} \]

\[ CL_{Total} = \frac{6.36 \frac{L}{h}}{0.2} = 31.8 \frac{L}{h} \]
d) Graph the plasma-concentration time profile for the first 24 hours when 1000mg of drug A are administered to T.T. via an IV bolus injection. Assume that the drug is immediately distributed throughout the body, crosses membranes easily, and that all elimination processes are first-order processes.

\[ Vd = 3L + 38L \times f_u \cdot f_{uT} = 3L + 38L \times 0.9 \times 0.05 = 687L \]

\[ k_e = \frac{31.8 L}{687L} = 0.0463 \frac{1}{h} \]

\[ C(t) = \frac{Dose}{VD} \cdot e^{-k_e \cdot t} = \frac{1000mg}{687L} \cdot e^{-0.0463 \cdot t} \]

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**Problem 3**

Which properties does a drug need to have in order to demonstrate the following? Explain briefly.

a) Active tubular secretion
b) Glomerula secretion
c) Passive tubular reabsorption

**Active tubular secretion:** As active transporters are mainly anionic or cationic transporters, drugs which are actively secreted must be bases or acids.

**Glomerula filtration:** Drugs which are filtrated must fall below a certain molecular weight size. I.e. proteins are not filtrated in the glomerulus because of their large molecular weight.
**Passive tubular reabsorption**: Neutral lipophilic drugs are reabsorbed easily. Passive tubular reabsorption of bases or acids depends on the pH of the urine. Hydrophilic drugs tend not be reabsorbed extensively.

Problem 4

TRUE (T) or FALSE (F)

For a high extraction drug, liver blood flow is important to both hepatic clearance and oral bioavailability.

T  F

For low extraction drug, $f_u$ (fraction of unbound drug in plasma) is important to both hepatic clearance and oral bioavailability.

T  F

Basic drugs that are polar in their unionized form, the extent of re-absorption depends on the degree of its ionization.

T  F

Secretion is indicated when renal clearance is larger than GFR*$f_u$.

T  F

It is possible for renal clearance to be close to the kidney blood flow.

T  F

Assuming no plasma protein binding, the renal clearance equals the urine flow when full reabsorption occurs.

T  F