**ADME_8_Clearance**

- **Clearance**: Clearance is the volume of plasma from which a drug is removed per given time unit. Since it involves volume per given time, the units for clearance are **mL per minute**, and clearance is usually abbreviated as **CL**. For example, if a drug has a clearance of 5 mL/min then that means that 5 mL of plasma loses the drug every minute.

- Let's first revisit the plasma drug concentration curve that was shown before. Recall that once an IV bolus is given, the plasma concentration of the declines over time. This decline has two phases. The initial decline is rapid and it is attributed to the **distribution** of the drug. The **second phase is due to drug clearance**.

![Plasma Drug Concentration Curve](image)

- **Total Clearance**: The major route of elimination is usually renal elimination followed by hepatic inactivation. So the **total clearance is actually a sum of renal clearance plus hepatic clearance plus other minor elimination routes**. Usually, other routes contribute very little to total clearance, so we typically say that the total clearance of a drug depends on renal and hepatic clearance. Therefore, blood flow to the kidneys and the liver is a critical factor, because the more blood flows through these organs the more plasma is cleared of a drug.

\[ CL_{total} = CL_{renal} + CL_{hepatic} + CL_{others} \]
• **Renal Clearance:** Renal clearance is the volume of plasma cleared of a drug or substance per given unit of time. As I already mentioned the unit of clearance is then volume per unit time or typically mL per min. So substances that have a high clearance value tend to be removed by the kidneys very efficiently and sometimes a single pass through the kidneys is enough. But drugs with low clearance values would take a while before they are removed. Renal clearance can be calculated by a simple equation shown below:

\[ CL = \frac{C_u V_u}{C_p} \]

- Basically the concentration of a drug in urine is divided by the plasma concentration of the drug and then the resulting fraction is multiplied by the urine flow rate. Since the concentration values cancel each other out, the resulting unit is mL per min.

• **Creatinine Clearance (CrCL):** Recall that creatinine is a byproduct of muscle breakdown. In most people this is produced at a fairly constant rate. The kidneys are the only source of creatinine elimination and it is mostly excreted by glomerular filtration, so unless there is change in production of creatinine, for example in a disease state or unless the kidneys are not functioning properly, the plasma concentration is usually within an expected range. In fact, plasma correlates well with CrCl, and plasma concentration of Cr is used to calculate CrCl in a patient. In turn CrCl is an indicator of kidney function. In an adult male, CrCl is roughly 100 mL per min, which means that every minute 100 ml of plasma is cleared of creatinine. Since Cr is eliminated mostly by by GF, we can estimate GFR from creatinine clearance. Creatinine clearance can be used as a benchmark to compare other drugs.
Clearance Ratio: The formula shown below allows us to compare renal clearance of drugs with creatinine clearance. If we know renal clearance for a given drug, we can divide it by the CrCl to derive a clearance ratio. If the ratio is 1 then that drug is cleared by GFR just like creatinine. If the ratio is more than 1 then it means that the drug is excreted by both GFR and tubular secretion. On the other hand if the ratio is less than one, then the drug is reabsorbed into the circulation following filtration. So this clearance ratio gives us an indication of the mechanism by which a drug is being eliminated by the kidneys.