Clearance

The clearance for an organ, such as the liver or kidney, that metabolizes or eliminates drugs is determined by the blood flow to the organ and the ability of the organ to metabolize or eliminate the drug. Liver blood flow (Q_H) and renal blood flow (Q_R) are each ~ 1–1.5 L/min in adults with normal cardiovascular function.

Extraction ratio (ER), The ability of an organ to remove or extract the drug from the blood or serum, which is the fraction of drug removed by the organ, and is computed by measuring the concentrations of the drug entering (Cin) and leaving (Cout) the organ:

$$ER = (C_{in} - C_{out})/C_{in}$$

$$F = 1 - ER$$

F: Bioavailability

Liver or renal blood flow and the extraction ratio for a drug are rarely measured in patients. However, the extraction ratio is oftentimes determined during the drug development process, and knowledge of this parameter can be extremely useful in determining how the pharmacokinetics of a drug will change during a drug interaction or if a patient develops hepatic, renal, or cardiac failure.

The drug clearance for an organ is equal to the product of the blood flow to the organ and the extraction ratio of the drug. Therefore, hepatic clearance (Cl_H) for a drug would be determined by taking the product of liver blood flow (Q_H) and the hepatic extraction ratio (ER_H) for the drug.

$$(Cl_H = Q \cdot ER_H)$$

And renal clearance (Cl_R) for a medication would be determined by multiplying renal blood flow (Q_R) and the renal extraction ratio for the agent

$$(Cl_R = Q \cdot ER_R)$$

The total clearance for a drug is the sum of the individual clearances for each organ that extracts the medication. For example, the total clearance (Cl) for a drug that is metabolized by the liver and eliminated by the kidney is the sum of hepatic and renal clearance for the agent:

$$Cl = Cl_H + Cl_R$$

Hepatic Clearance:

There are three main factors affecting the hepatic clearance :

1. Intrinsic ability of the enzyme to metabolize a drug (intrinsic clearance)
2. The fraction of drug present in the bloodstream that is not bound to cells or proteins, such as albumin, α1-acid glycoprotein, or lipoproteins, but is present in the unbound, or "free," state (unbound fraction of drug);
3. Liver blood flow

$$ER = \frac{f_u CL_{int}}{Q + f_u CL_{int}}$$

Where:
(Q_R) :blood flow to the liver,
(*fu*) :the fraction of drug not bound to plasma proteins, and
(*CLint*) :intrinsic clearance

Also, $$(Cl_H = Q \cdot ER_H)$$

Therefore:

$$CL_H = Q\left[\frac{f_u CL_{int}}{Q + f_u CL_{int}}\right]$$

Two limiting cases arise

1. ***when fuCLint << Q:***

For drugs with a low hepatic extraction ratio (extraction ratios <0.3.), hepatic clearance is mainly a product of the free fraction of the drug in the blood or serum and intrinsic clearance.
The equation can be simplified to:

$$CL_H = f_u CL_{int}$$

Notes:

- In this case, drug interactions that displace drug molecules bound to proteins will increase the fraction of unbound drug in the blood (↑fu); more unbound drug molecules will be able to leave the vascular system (drug-protein complexes are far too big to exit the vascular system) and enter hepatocytes where the additional unbound drug will be metabolized and hepatic drug clearance will increase.

- Additionally, drug interactions that inhibit or induce the cytochrome P-450 enzyme system (decreasing or increasing Cl′int, respectively) will change the hepatic clearance of the medication accordingly.

- The hepatic clearance of drugs with low extraction ratios does not change much when liver blood flow decreases secondary to liver or cardiac disease.

- Examples of drugs with low hepatic extraction ratios are valproic acid, phenytoin, and warfarin.

2. ***When fuCLint >> Q***

For drugs with high hepatic extraction ratios(extraction ratios >0.7), hepatic clearance is mainly a function of liver blood flow and the equation can be reduced to:

$$CL_H = Q$$

Notes:

- The rate limiting step for drug metabolism in this case is how much drug can be delivered to the liver because the capacity to metabolize drug is very large.

- In this case, hepatic clearance is very sensitive to changes in liver blood flow due to congestive heart failure or liver disease.

- However, the hepatic clearance of drugs with high extraction ratios does not change much when protein binding displacement or enzyme induction or inhibition occurs due to drug interactions.

- Examples of drugs with high hepatic extraction ratios are lidocaine, morphine, and most tricyclic antidepressants.

Renal Clearance

The physiological determinants of renal clearance are :

1. Glomerular filtration rate (GFR)
2. The free fraction of drug in the blood or serum (f*u*)
3. The clearance of drug via renal tubular secretion (Clsec)
4. The fraction of drug reabsorbed in the kidney (FR)

$$Cl_R = [(f_u \cdot GFR) + Cl_{sec}](1 - FR)$$

Also:

$$Cl_{R_{sec}} = Q\left[\frac{f_u CL_{int}}{Q + f_u CL_{int}}\right]$$

Therefore:

$$Cl_R = \left[(f_u \cdot GFR) + \frac{Q_R \cdot (f_u Cl'_{sec})}{Q_R + (f_u Cl'_{sec})} \right] (1 - FR)$$

Note:

- If the renal clearance of a drug is greater than glomerular filtration rate, it is likely that the drug was eliminated, in part, by active tubular secretion. The aminoglycoside antibiotics and vancomycin are eliminated primarily by glomerular filtration. Digoxin, procainamide, ranitidine, and ciprofloxacin are eliminated by both glomerular filtration and active tubular secretion.

Clinical Assessment of Renal Function

- In some cases, glomerular filtration rate and renal tubular secretion function may be measured in patients with renal disease. However, for the purposes of drug dosing, glomerular filtration rate is approximated by measuring or estimating creatinine clearance for a patient. Creatinine is a by-product of muscle metabolism that is eliminated primarily by glomerular filtration.

- In routine clinical practice, it is not practical to collect the urine samples that are needed to measure creatinine clearance directly. However, creatinine clearance in adult patients can be estimated either from a standard nomogram or from equations such as that proposed by Cockcroft and Gault

  For men, creatinine clearance can be estimated from this equation as follows:

$$CL_{CR}\,(\text{mL/min}) = \frac{(140 - \text{age})(\text{weight in kg})}{72(\text{serum creatinine in mg/dL})}$$

  For women multiply the equation by 85% (0.85).

- Creatinine clearance overestimates true glomerular filtration rate (GFR) as measured by inulin clearance because creatinine is secreted by the renal tubule in addition to being filtered at the glomerulus.

- The overestimation increases as GFR declines from 120 to 10 mL/min/1.73 m^2, ranging from a 10–15% overestimation with normal GFR to a 140% overestimation when GFR falls below 10 mL/min.

- Serum creatinine does not start to rise until GFR falls to 50 mL/min because increasing tubular secretion of creatinine offsets the decline in its glomerular filtration.

- The Cockcroft and Gault equation also overestimates glomerular filtration rate in patients with low creatinine production due to cirrhosis or cachexia and may be misleading in patients with rapidly changing renal function. In these situations, accurate estimates of creatinine clearance can only be obtained by actually measuring urine creatinine excretion rate in a carefully timed urine specimen.

- The Cockcroft and Gault equation cannot be used to estimate creatinine clearance in pediatric patients because muscle mass has not reached the adult proportion of body weight. Therefore, Schwartz and colleagues developed the following equation to predict creatinine clearance in these patients:

$$CL_{CR}\,(\text{mL/min/1.73 m}^2) = \frac{k \cdot L\ (\text{in cm})}{\text{plasma creatinine in mg/dL}}$$

where L is body length and k varies by age and sex as follows:
Neonates to children 1 year of age: $k = 0.45$
Children 1–13 years of age: $k = 0.55$
Females 13–20 years of age: $k = 0.57$
Males 13–20 years of age: $k = 0.70$