

Renal Clearance: General Notes

J. Stark

Cl_{Ren} depends on glomerular filtration rate (GFR), tubular reabsorption, and tubular secretion. (In addition to urinary secretion, there is also biliary, pulmonary, and salivary excretion. Each of these will contribute a clearance term to the total body clearance).

When working Cl_{Ren} problems, there are three important numbers to remember:

*Renal blood flow (RBF) = 1200 ml/min

*Glomerular filtration rate (GFR) = 125 ml/min

*Urine flow = 1.5 ml/min.

(Some books may also discuss renal plasma flow and other parameters. For this course, only the three above will be used in calculations).

1) Glomerular filtration.

Glomerular filtration is passive filtration of the blood as blood flows through the glomeruli of the kidney. The extent to which a drug is filtered depends on the molecular size, protein binding, ionization, polarity, and kidney function in general. If Cl_{Ren} depends only on filtration,

$$Cl_{Ren} = GFR * f_u,$$

where f_u is the unbound fraction of drug and GFR is the glomerular filtration rate. As given above, the normal GFR is 125 ml/min. If this number is compared to the renal blood flow, RBF = 1200 ml/min, it becomes obvious that only 11% of the blood is filtered:

$$(125/1200) * (100) = 11\%.$$

For individual patients with some renal dysfunction, the GFR is often determined from the creatinine clearance. Creatinine is eliminated only by glomerular filtration and has no protein binding ($f_u = 1$). So for creatinine,

$$Cl_{Ren} = GFR.$$

Determining GFR will be very important when administering a drug whose principal means of elimination is via glomerular filtration.

2) Tubular secretion.

Tubular secretion can increase the Cl_{Ren} by actively secreting the drug (as opposed to only the passive diffusion in glomerular filtration). The rate of secretion depends on the transporter. If the transporter is slow, the secretion will depend on f_u . Very efficient active transport (and an absence of any reabsorption) can lead to a maximum renal clearance of

$$Cl_{Ren} = RBF.$$

This is the upper limit for renal clearance.

3) Tubular reabsorption.

Some drugs may be reabsorbed after being filtered out of the blood. Thus, the Cl_{Ren} may be smaller than expected (when considering only filtration and $Cl_{Ren} = GFR * fu$). If a drug is “completely” reabsorbed after filtration and no active secretion takes place, the renal clearance will be limited to the amount of drug that leaves the kidney as the urine flows into the bladder. In this extreme case,

$$\begin{aligned} Cl_{Ren} &= (\text{urine flow}) * fu \\ &= 1.5 \text{ ml/min} * fu. \end{aligned}$$

Thus, $Cl_{Ren} \ll GFR * fu$.

(This is for reabsorption via passive diffusion. If reabsorption occurs via active transport, Cl_{Ren} may approach zero).

Examples.

Explain the clearance observed for each of the following drugs.

Drug		f_u		Cl_{Ren}
A		0.5		10.0
B		0.1		0.15
C		0.02		20.0

Drug A.

Ask yourself, “What would the renal clearance be if the Cl_{Ren} depended only on glomerular filtration?”

$$\begin{aligned} Cl_{Ren} &= GFR * fu \\ &= (125 \text{ ml/min}) * (0.5) \\ &= 62.5 \text{ ml/min.} \end{aligned}$$

The actual value ($Cl_{Ren} = 10 \text{ ml/min}$) is lower than this calculated value based only on filtration, i.e. less drug is being removed from the body than we expected. Thus, reabsorption must be taking place.

Drug B.

This drug has a very low renal clearance; If only filtration takes place, we expect to see

$$\begin{aligned} Cl_{Ren} &= GFR * fu \\ &= (125 \text{ ml/min}) * (0.1) \\ &= 12.5 \text{ ml/min.} \end{aligned}$$

Again, reabsorption must be taking place. To what extent?

Recall that if a drug is completely reabsorbed and is not actively secreted,

$$Cl_{Ren} = \text{urine flow} * fu$$

For drug B this would be

$$\begin{aligned} Cl_{Ren} &= (1.5 \text{ ml/min}) * (0.1) \\ &= 0.15 \text{ ml/min.} \end{aligned}$$

This is exactly what was given in the data table for drug B. Therefore, we know that this drug is completely absorbed and is not actively secreted.

Note: If Cl_{Ren} were important for the elimination of this drug, we would expect a very large half-life since elimination is slow.

Drug C.

Look at the information given and compare drugs A and C. For Drug C we see a very low f_u (i.e. almost all of the drug is bound to plasma proteins) and yet the Cl_{Ren} is larger than that for Drug A. If Drug C is eliminated only by glomerular filtration, we expect

$$\begin{aligned} Cl_{Ren} &= GFR * f_u \\ &= (125 \text{ ml/min}) * (0.02) \\ &= 2.5 \text{ ml/min.} \end{aligned}$$

This is much lower than the experimental value of 20 ml/min. Thus, the drug must be actively secreted.

Does reabsorption occur for this drug?

Possibly. All that can be said is that if reabsorption does take place, the amount reabsorbed is much smaller than the amount actively secreted.

More Examples.

Given: A drug has exhibits no plasma protein binding and has a renal clearance of 125 ml/min.

Is this drug being reabsorbed?

Possibly. However, if the drug is reabsorbed, it must be secreted to the same extent in order to achieve $Cl_{Ren} = 125 \text{ ml/min}$.

What about a drug with the same renal clearance but with 25% binding to plasma proteins?

Here, f_u is 0.75. So the clearance due to filtration will be less than GFR ($< 125 \text{ ml/min}$ since $Cl_{Ren} = GFR * f_u$). Therefore, we can say that reabsorption may occur but that secretion occurs to a greater degree (increasing the Cl_{Ren} and counter-acting the reabsorption process).