

PHAR 7632 Chapter 16

Routes of Excretion

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Routes of Excretion

Student Objectives for this Chapter

After completing the material in this chapter each student should:-

- be able to describe the various routes by which a drug may be excreted from the body
- understand the parameter renal clearance and its relationship with the excretion processes in the kidney
- understand the influence of renal disease on drug elimination
- be able to calculate suitable drug dosage regimen for patients with impaired renal function based on a $\overline{C_p}$ or a $C_{p_{min}}/C_{p_{max}}$ approach

The major routes of drug excretion described in this Chapter are renal, biliary, pulmonary and salivary.

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Renal Excretion

The major organ for the excretion of drugs is the KIDNEY. The functional unit of the kidney is the nephron and components of the nephron include Bowman's capsule, Proximal Tubule, Loop of Henle, Distal Tubule and the Collecting Duct. Low molecular weight molecules are filtered in Bowman's capsule. Active secretion of weak electrolyte drugs (acids) and reabsorption of water occurs in the proximal tubules. Additional reabsorption of water occurs in the Loop of Henle. Passive reabsorption of water and lipid soluble drugs occur in the distal tubule.

There are three major renal excretion processes to consider; 1) glomerular filtration; 2) tubular secretion; and 3) tubular re-absorption

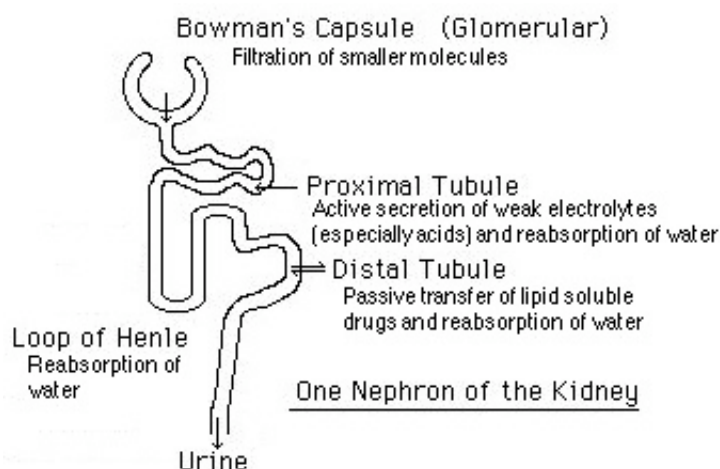


Figure 16.2.1 One Nephron of the Kidney

Glomerular Filtration

In the glomerular all molecules of low molecular weight ($< 60,000$ Dalton) are filtered out of the blood. Most drugs are readily filtered from the blood unless they are tightly bound to large molecules such as plasma protein or have been incorporated into red blood cells. The glomerular filtration rate varies from individual to individual but in healthy individuals the normal range is 110 to 130 ml/min (≈ 180 L/day). About 10% of the blood which enters the glomerular is filtered. This filtration rate is often measured by determining the renal clearance of inulin. Inulin is readily filtered in the glomerular, and is not subject to tubular secretion or re-absorption. Thus inulin clearance is equal to the glomerular filtration rate.

Again, most drugs are filtered from blood in the glomerular, the overall renal excretion however is controlled by what happens in the tubules. More than 90% of the filtrate is reabsorbed. 120 ml/min is 173 L/day. Normal urine output as you may realize is much less than this, about 1 to 2 liter per day.

Tubular secretion

In the proximal tubule there is re-absorption of water and active secretion of some weak electrolyte but especially weak acids. As this process is an active secretion it requires a carrier and a supply of energy. This may be a significant pathway for some compounds such

as penicillins. Because tubular secretion is an active process there may be competitive inhibition of the secretion of one compound by another. A common example of this phenomena is the inhibition of penicillin excretion by competition with probenecid. When penicillin was first used it was expensive and in short supply, thus probenecid was used to reduce the excretion of the penicillin and thereby prolong penicillin plasma concentrations (PDR). Since then it has been shown that probenecid also alters the distribution of penicillins to various tissues causing more drug to distribute out of plasma, causing even less to be eliminated. This could also be used to reduce the excretion of cephalosporins.

Drugs or compounds which are extensively secreted, such as *p*-aminohippuric acid (PAH), may have clearance values approaching the renal plasma flow rate of 425 to 650 ml/min, and are used clinically to measure this physiological parameter (see Documenta Geigy).

Tubular re-absorption

In the distal tubule there is passive excretion and re-absorption of lipid soluble drugs. Drugs which are present in the glomerular filtrate can be reabsorbed in the tubules. The membrane is readily permeable to lipids so filtered lipid soluble substances are extensively reabsorbed. A reason for this is that much of the water, in the filtrate, has been reabsorbed and therefore the concentration gradient is now in the direction of re-absorption. Thus if a drug is non-ionized or in the unionized form it may be readily reabsorbed.

Many drugs are either weak bases or acids and therefore the pH of the filtrate can greatly influence the extent of tubular re-absorption for many drugs. When urine is acidic weak acid drugs tend to be reabsorbed. Alternatively when urine is more alkaline, weak bases are more extensively reabsorbed. Making the urine more acidic can cause less reabsorption of weak bases or enhanced excretion. These changes can be quite significant as urine pH can vary from 4.5 to 8.0 depending on the diet (e.g. meat can cause a more acidic urine) or drugs (which can increase or decrease urine pH).

In the case of a drug overdose it is possible to increase the excretion of some drugs by suitable adjustment of urine pH. For example, in the case of pentobarbital (a weak acid) overdose it may be possible to increase drug excretion by making the urine more alkaline with sodium bicarbonate injection.

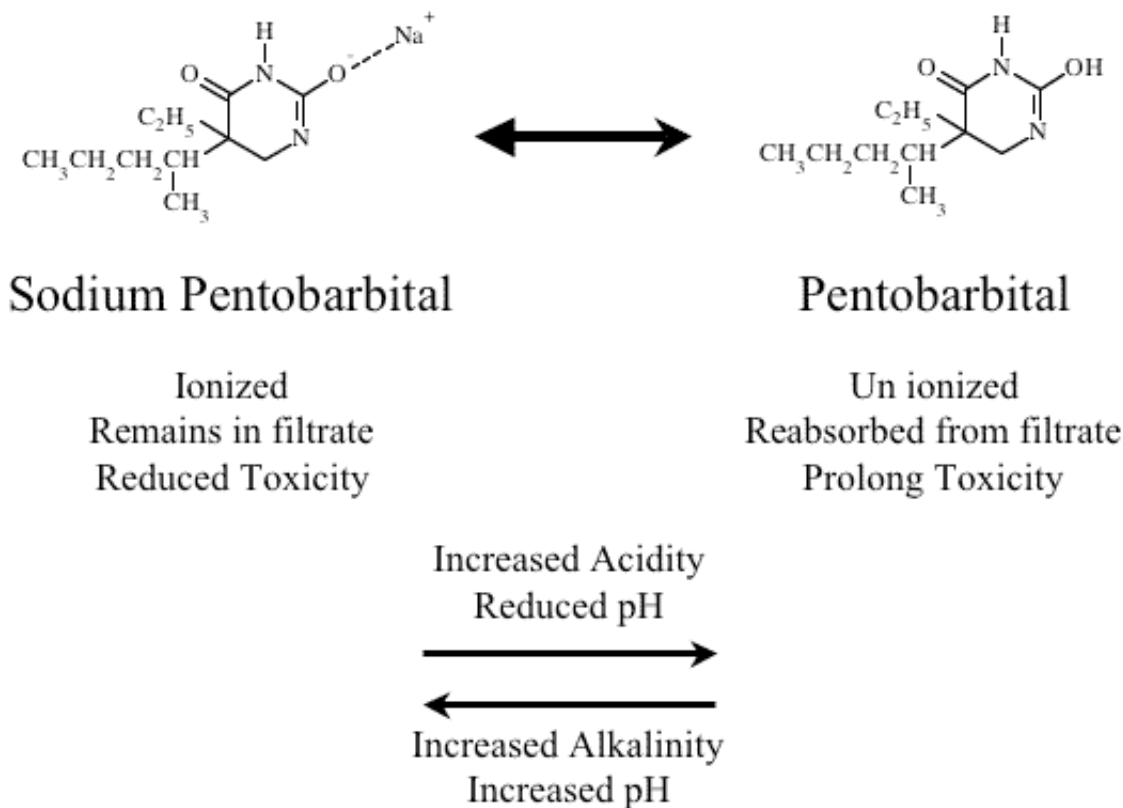


Figure 16.2.2 Pentobarbital Ionization

This method is quite effective if the drug is extensively excreted as the unchanged drug (i.e. f_e approaches 1). If the drug is

extensively metabolized then alteration of kidney excretion will not alter the overall drug metabolism all that much.

The effect of pH change on tubular re-absorption can be predicted by consideration of drug pKa according to the Henderson-Hasselbalch equation.

Renal clearance

One method of quantitatively describing the renal excretion of drugs is by means of the renal clearance value for the drug. Renal clearance relates the rate of excretion, $\Delta U/\Delta t$, to drug concentration. Units are ml/min.

$$\text{Rate of Excretion} = \frac{\Delta U}{\Delta t} = CL_{renal} \cdot C_p$$

Equation 16.2.1 Rate of Excretion

Remember that renal clearance can be calculated as part of the total body clearance for a particular drug. Renal clearance can be used to investigate the mechanism of drug excretion. If the drug is filtered but not secreted or reabsorbed the renal clearance will be about 120 ml/min in normal subjects. If the renal clearance is less than 120 ml/min then we can assume that at least two processes are in operation, glomerular filtration and tubular re-absorption. If the renal clearance is greater than 120 ml/min then tubular secretion must be contributing to the elimination process. It is also possible that all three processes are occurring simultaneously. The drug renal clearance value can be compared with physiologically significant values, e.g. glomerular filtration rate (GFR) of approximately 120 ml/min or renal plasma flow of about 650 ml/min.

Renal clearance is then:

$$CL_{renal} = \frac{\text{filtration rate} + \text{secretion rate} - \text{reabsorption rate}}{C_p}$$

Equation 16.2.2 Renal Clearance

Renal clearance values can range from 0 ml/min, the normal value for glucose which is usually completely reabsorbed to a value equal to the renal plasma flow of about 650 ml/min for compounds like *p*-aminohippuric acid.

We can calculate renal clearance using the pharmacokinetic parameters k_e and V . Thus $CL_{renal} = k_e \cdot V$. Renal clearance can also be determined as U^∞/AUC . We can calculate renal clearance by measuring the total amount of drug excreted over some time interval and dividing by the plasma concentration measured at the midpoint of the time interval. (This was part of a laboratory experiments-[first beaker experiment](#)).

$$\text{Renal Clearance} = \frac{\text{Rate of Excretion}}{\text{Plasma Concentration}}$$

Equation 16.2.3 Renal Clearance

$$\text{Renal Clearance} = CL_{renal} = \frac{\Delta U/\Delta t}{C_{p_{midpoint}}}$$

Equation 16.2.4 Renal Clearance

To continue we can briefly look at some other routes of drug excretion. We will then return to the topic of renal excretion by considering drug dosage adjustments in patients with reduced renal function.

References

- [How the Kidney Works](#) by Stephen Z. Fadem, M.D., FACP
 - [The Kidney](#) at Wikipedia
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Hemodialysis

Hemodialysis or 'artificial kidney' therapy is used in renal failure to remove toxic waste material normally removed by the kidneys, from the patient's blood. In the procedure blood is diverted externally and allowed to flow across a semi-permeable membrane that is bathed with an aqueous isotonic solution. Small molecules including nitrogenous waste products and some drugs will diffuse from the blood, thus these compounds will be eliminated. Therefore in patients with kidney failure, hemodialysis may be an important route of drug elimination.

This technique is particularly important with drugs which:

1. are smaller (< 500) molecular weight; and
2. are not tightly bound to plasma protein;
3. have a small apparent volume of distribution.
4. have good water solubility;

Conversely drugs which are tightly bound or extensively stored or distributed into tissues are only poorly removed by this route, or process.

A simulation of drug concentration with and without dialysis is shown in Figure 16.3.1.

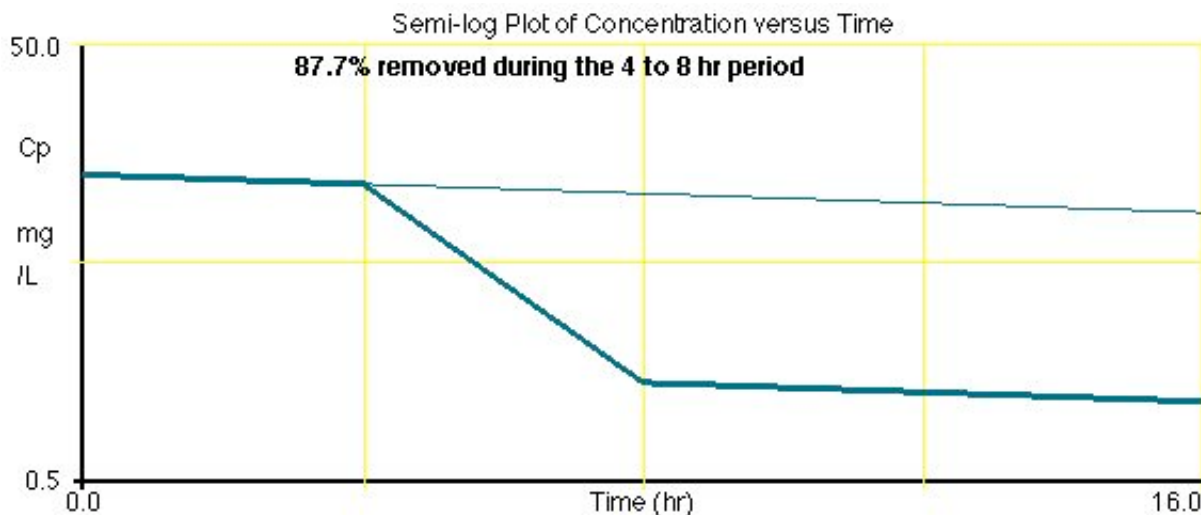


Figure 16.3.1 Drug Concentration before, during and after Low Flux Dialysis

Click on the figure to view the Java Applet window
 Java Applet as a [Linear Plot](#)

Low flux hemodialysis will readily remove molecules smaller than 500 Dalton. As the molecular weight increases to approximately 1000 Dalton the amount removed steadily decreases to insignificant. Thus clearance by hemodialysis falls from a maximum of about 4 L/hr to near zero with higher molecular weight compounds. Hemodialysis clearance is converted to a rate constant by dividing by the apparent volume distribution. This rate constant is added to the patient's elimination rate constant to give the increased, apparent rate constant during hemodialysis. As can be seen in Figure 16.3.1 this can cause an increased removal of a drug. This can be useful in

cases where the concentration is too high but it can also complicate the maintenance of therapeutic concentrations. In [Chapter 14](#) and [15](#) drug dosage regimens were calculated using elimination rate constant and volume of distribution. Hemodialysis can mean a significant increase in the amount of drug removed during the dialysis period. An additional dose may be required. Later in this chapter we will adjust dosage regimens for reduced renal function according to $C_{p_{average}}$ or $C_{p_{min}}/C_{p_{max}}$ requirements

Item 1. Hemodialysis may contribute significantly to the elimination of some drugs in patients with poor renal function. Explore the effect of molecular weight, protein binding and apparent volume of distribution on dialysis and explore the need for a post-dialysis dose. [Explore the problem as a Linear Plot - Java Applet](#)

References

- Shargel, L. and Yu, A.B.C. 1999 "Applied Biopharmaceutics and Pharmacokinetics", 4th ed., Appleton-Century-Crofts, Norwalk, CT, page 556, table 18.6
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Biliary Excretion

The liver secretes 0.25 to 1 liter of bile each day. Some drugs and/or their metabolites are excreted by the liver into bile. Anions, cations, and non-ionized molecules containing both polar and lipophilic groups are excreted into the bile provided that the molecular weight is greater than about 300 Dalton. Molecular weights around 500 Dalton appears optimal for biliary excretion in humans. Lower molecular weight compounds are reabsorbed before being excreted from the bile duct. Conjugates, glucuronides (drug metabolites) are often of sufficient molecular weight for biliary excretion. This can lead to biliary recycling. Indomethacin is one compound which undergoes this form of recycling.

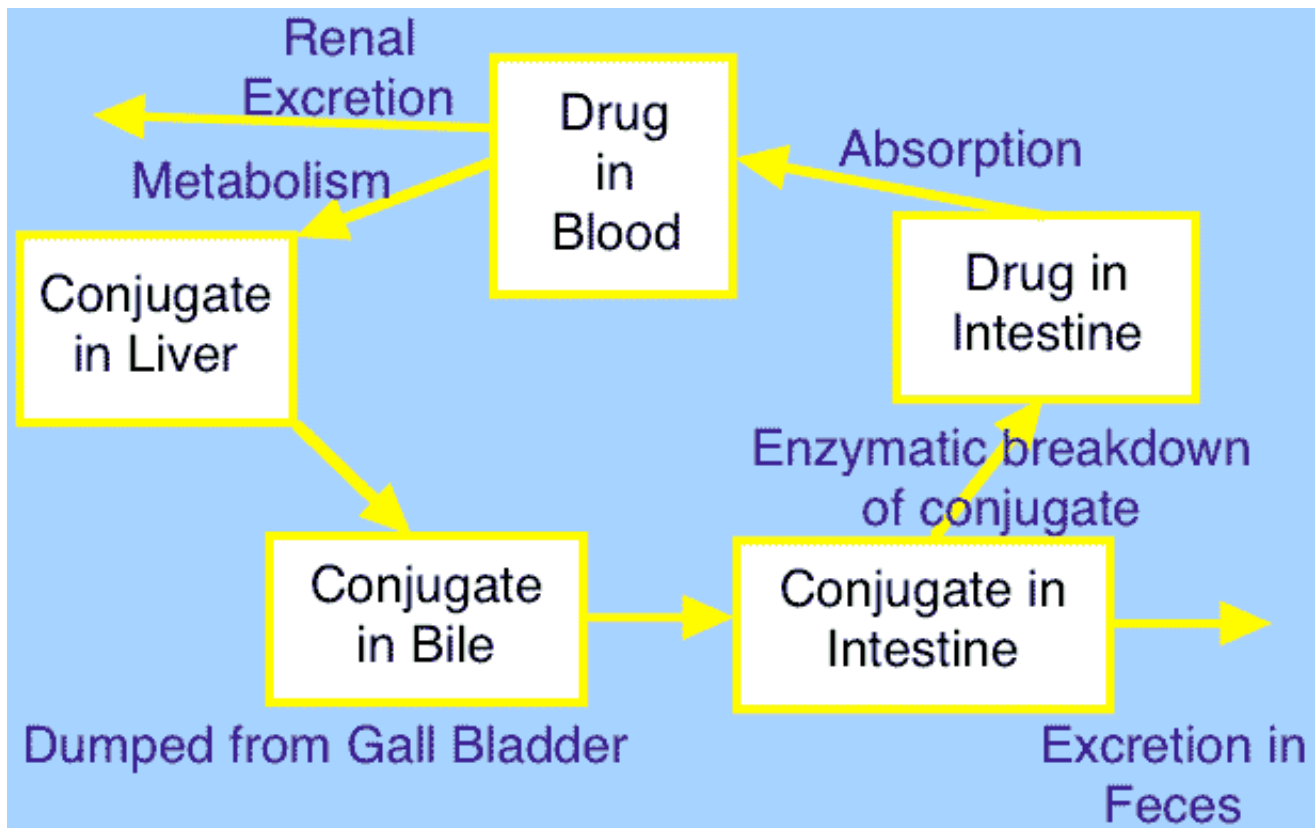


Figure 16.4.1 Enteroheptic Recycling

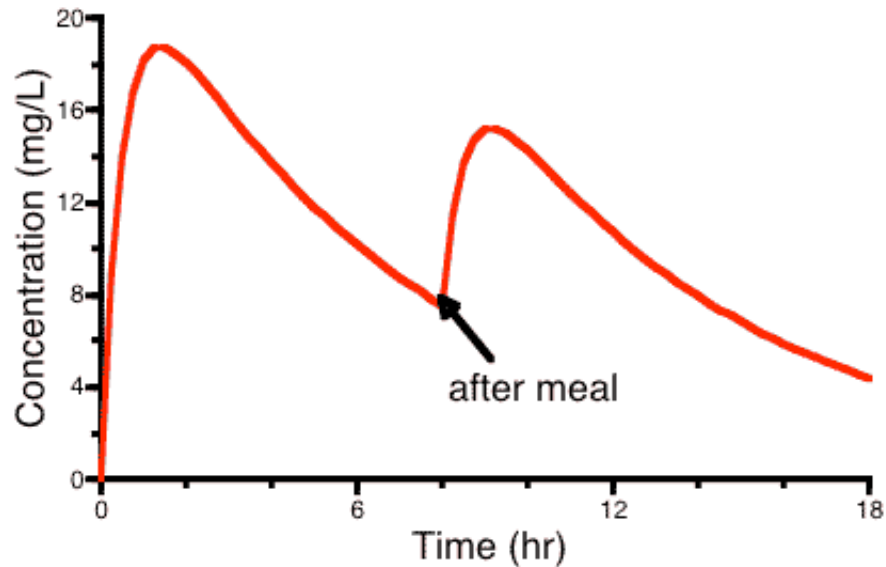


Figure 16.4.2 C_p versus Time showing a Second Peak

Figure 16.4.2 illustrate plasma concentration *versus* time curve which may result from extensive enterohepatic recycling. Note, the presence of the second peak shortly after the dumping of bile into the small intestine in response to the presence of food.

Other compounds extensively excreted in bile include cromoglycate (unchanged drug), morphine, and chloramphenicol (as glucuronide). At least part of the biliary secretion is active since bile/plasma concentrations maybe as high as 50/1. There can also be competition between compounds.

The efficiency of this biliary excretion system can be assessed by use of a test substance, such as Bromsulphalein.

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Pulmonary Excretion

The lung is the major organ of excretion for gaseous and volatile substances. Most of the gaseous anesthetics are extensively eliminated in expired air.

The breathalyzer test is based on a quantitative pulmonary excretion of ethanol.

[How a Breathalyzer works](#)

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Salivary Excretion

Saliva volume is typically one to two liters per day with flow rates ranging from 0.5 ml/min to more than 10 times that in the presence or thought of food. Saliva pH commonly ranges between 7.4 and 6.2 although lower values are possible. Saliva also contains a number of enzymes including amylase, ptylin, lipase, and esterases.

Salivary excretion is not really a method of drug excretion as the drug will usually be swallowed and reabsorbed, thus a form of 'salivary recycling'. Drug excretion into saliva appears to be dependent on pH partition and protein binding. In many cases salivary concentration represents the free drug concentration in plasma. This mechanism appears attractive in terms of drug monitoring, that is determining drug concentration to assist in drug dosage adjustment. For some drugs, the saliva/free plasma ratio is fairly constant. Therefore drug concentrations in saliva could be a good indication of drug concentration in plasma. For some drugs localized side effects maybe due to salivary excretion of the drug. Pharmacokinetic studies in special populations may be more feasible using saliva concentrations.

References

- Washington, N., Washington C. and Wilson, C.G. 2001 **Physiological Pharmaceutics, Barriers to Drug Absorption**, Taylor and Francis, Inc., New York, NY ISBN 0-748-40562-3

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Renal Disease Considerations

Getting back to the renal excretion of drugs. If a drug is extensively excreted unchanged into urine (i.e. f_e closer to 1), alteration of renal function will extensively alter the drug elimination rate. Fortunately creatinine or inulin clearance can be used as a measure of renal function. For most drugs which are excreted extensively as unchanged drug it has been found that there is a good correlation between creatinine or inulin clearance and drug clearance or observed renal clearance and elimination rate (since V is usually unchanged).

Dose adjustment

Creatinine clearance

Creatinine is produced in the body by muscle metabolism from creatine phosphate. Creatinine production is dependent on the age, weight, and sex of the patient. Elimination of creatinine is mainly by glomerular filtration (> 90%) with a small percentage by active secretion. With the patient in stable condition the production is like a continuous infusion to steady state with the infusion rate controlled by muscle metabolism and the elimination controlled by renal function. Thus as renal function is reduced serum creatinine concentrations increases. Other compounds such as inulin are also used for GFR measurement. Although inulin GFR values are probably more accurate they involve administration of inulin and careful collection of urine for inulin determination. The major advantage of creatinine is that its formation is endogenous. Determination of creatinine clearance consists of collection of total urine and a plasma/serum determination at the mid-point time. Thus:

$$\text{Creatinine Clearance} = \frac{\text{rate of excretion into urine}}{\text{serum concentration}}$$

Equation 16.7.1 Creatinine Clearance

with serum creatinine expressed as mg/100 ml and creatinine clearance as ml/min. Normal inulin clearance values are 124 ml/min for men and 109 ml/min for women (Documenta Geigy, 1970). Because of some small renal secretion of creatinine, normal values of creatinine clearance are slightly higher than GFR measured with inulin. Thus, normal creatinine clearance values are about 120 to 130 ml/min.

Various investigators have developed equations which allow calculation of creatinine clearance using serum creatinine values. Thus a single serum level may be used when renal condition is stable. One commonly used equation is that of Cockcroft and Gault.

Males:

$$CL_{Cr} = \frac{[140 - \text{age}(\text{yr})] \bullet \text{body weight (kg)}}{72 \bullet C_{sCr}}$$

Equation 16.7.2 Creatinine Clearance

Females: Use 85% of the value calculated for males. C_r is the serum creatinine concentration in mg/dl. The original authors of this

equation used actual body weight in Equation 16.7.2. More recently it has been recommended that ideal body (IBW) be used in this equation unless the actual body weight (ABW) is less (Murphy, 2001). Generally use lean body weight in this equation as creatinine is formed in muscle (Shargel and Yu, 1985).

Estimation of k_{el} in a patient

The relationship between creatinine clearance and overall drug elimination can be easily seen by looking at plots of k_{el} observed versus creatinine clearance.

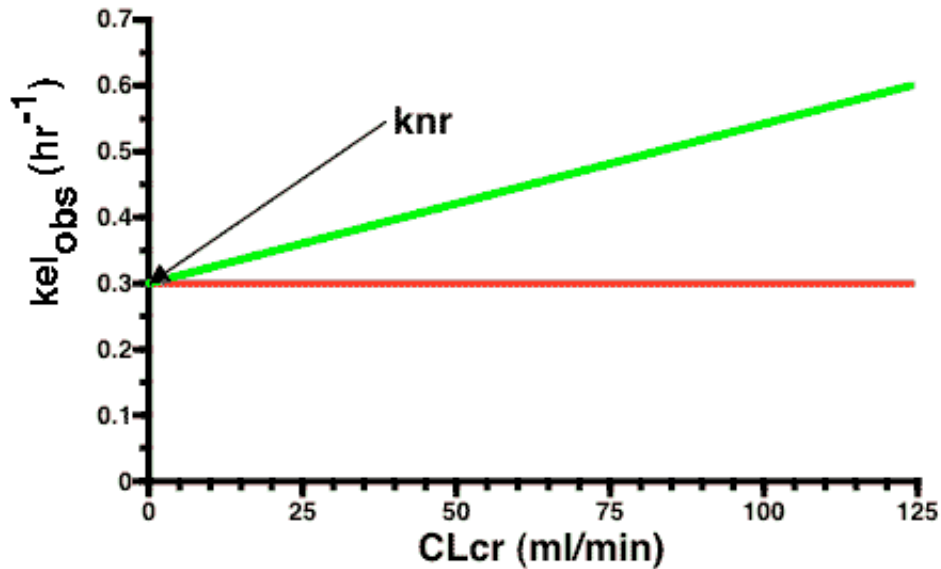


Figure 16.7.1 Plot of k_{el} versus CLCR (Dettli Plot)

These are often called Dettli plots.

Figure 16.7.1 shows the situation with considerable excretion as unchanged drug. i.e. f_e between 0.3 and 0.7.

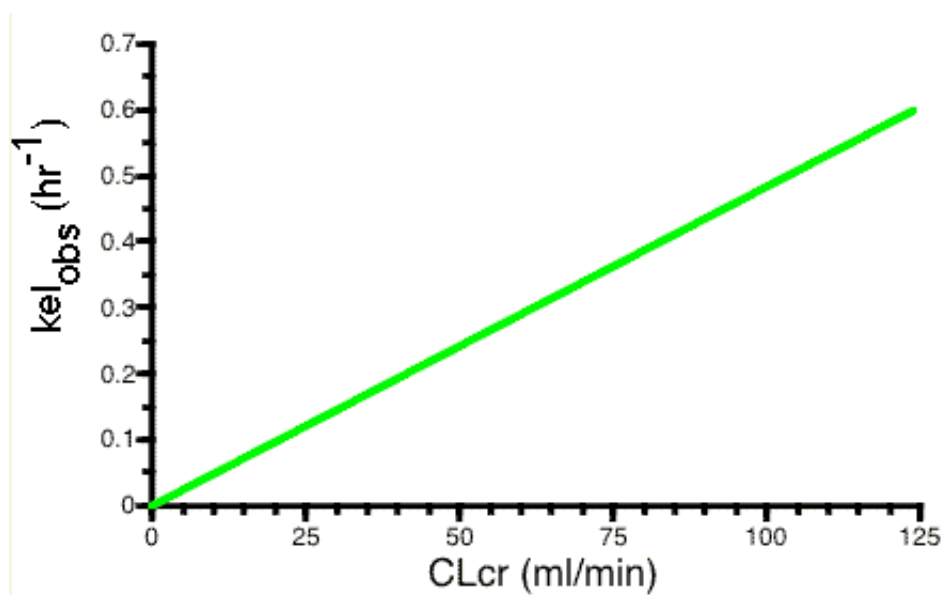


Figure 16.7.2 Dettli Plot ($f_e = 1$)

In Figure 16.7.2 drug is excreted entirely as unchanged drug. i.e. $f_e = 1$

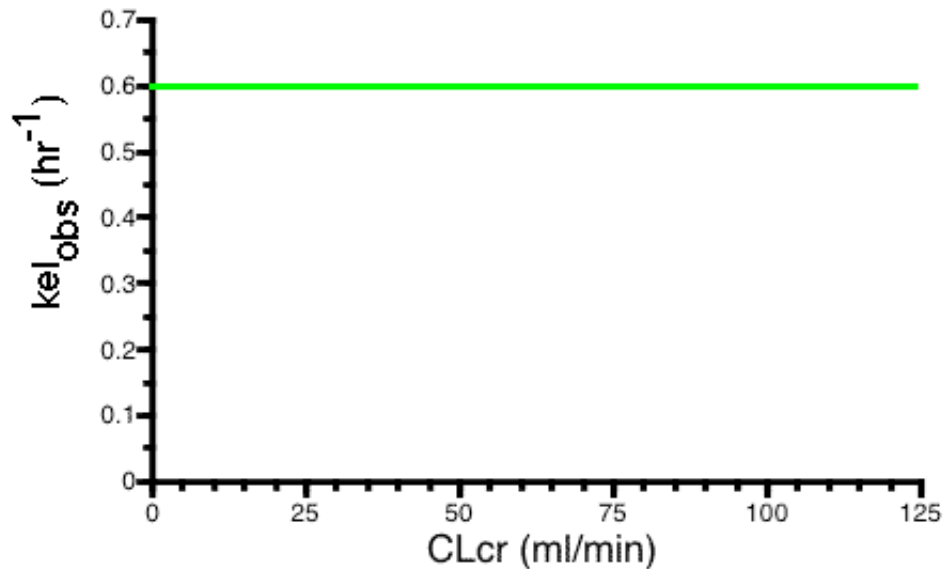


Figure 16.7.3 Dettli Plot ($f_e = 0$)

In Figure 16.7.3 drug is excretion only as metabolized drug, i.e. $f_e = 0$

We can use this information to calculate initial dosage regimens for patients taking drugs with high (> 0.25) f_e values. The first step is to estimate the creatinine clearance in the patient from their serum creatinine value. From a Dettli plot (k_{el} versus CL_{cr}) constructed from previous studies with this drug we can estimate the elimination rate constant in this patient. We can therefore calculate an optimum dose and dosing interval to achieve the desired average drug concentration or maximum or minimum drug concentrations. The Dettli plot may be built into a computer program or nomogram.

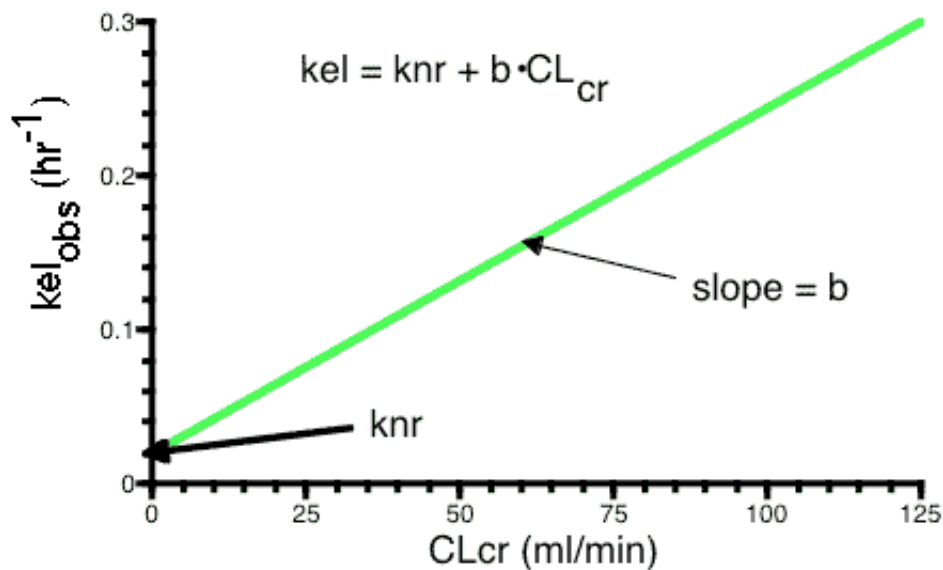


Figure 16.7.4 Dettli Plot Showing k_{el} Observed versus CL_{cr}

This is the plot shown before. In the references shown below there is information useful for calculating k_{el} in patients with impaired renal function.

Table 16.7.1 Some Example Values (Wagner, 1975)

	knr	b
Kanamycin	0.01	0.0024
Sulfadiazine	0.03	0.0005
Tetracycline	0.008	0.00072

As an example these data could be used to calculate the k_{el} for a patient with a CLcr of 10 ml/min compared a subject with normal renal function of 120 ml/min

For kanamycin

$$k_{el_{patient}} = knr + b \cdot CLcr = 0.01 + 0.0024 \times 10 = 0.01 + 0.024 = 0.034 \text{ hr}^{-1}$$

Compare this with the value for the normal subject: $k_{el} = 0.01 + 0.0024 \times 120 = 0.298 \text{ hr}^{-1}$

For sulfadiazine

$$k_{el_{patient}} = 0.03 + 0.0005 \times 10 = 0.03 + 0.005 = 0.035 \text{ hr}^{-1}$$

Compare this with the value for the normal subject: $k_{el} = 0.03 + 0.0005 \times 120 = 0.09 \text{ hr}^{-1}$

For tetracycline

$$k_{el_{patient}} = 0.008 + 0.00072 \times 10 = 0.008 + 0.0072 = 0.0152 \text{ hr}^{-1}$$

Compare this with the value for the normal subject: $k_{el} = 0.008 + 0.00072 \times 120 = 0.0944 \text{ hr}^{-1}$

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- Shargel, L. and Yu, A.B.C. 1985 **Applied Biopharmaceutics and Pharmacokinetics**, 2nd ed., Appleton-Century-Crofts, Norwalk, CT, page 312
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$C_{p\text{average}}$ Calculations

For patients with poor renal function taking drugs with high k_{el} values, dosage regimen adjustment is essential. Drugs that are eliminated via the kidneys will have reduced elimination in patients with impaired renal function. Steady state and average drug concentration will rise dangerously unless the dosage regimen is adjusted. One way to make this adjustment is to adjust the dose or dosing interval to maintain a required average drug concentration. For example consider the drug kanamycin. A patient of 70 kg with normal kidney function may receive 250 mg IM every six hours (about 3 half-lives; $t_{1/2} = 2.3$ hours). If $F = 1.0$ and $V = 13.3$ liter, $k_{el} = 0.693/2.3 = 0.30 \text{ hr}^{-1}$.

Then

$$\overline{C_p} = \frac{F \bullet Dose}{V \bullet k_{el} \bullet \tau} = \frac{1 \times 250}{13.3 \times 0.3 \times 6} = 10.4 \text{ mg/L}$$

Equation 16.8.1 Average Drug Concentration

If we assume that $k_a \gg k_{el}$ then

$$C_{p_{min}} = \frac{F \bullet Dose}{V} \bullet \left[\frac{R}{1 - R} \right]$$

where $R = e^{-0.3 \cdot 6} = 0.165$

Thus, $C_{p_{min}} = 3.7 \text{ mg/L}$

These are the results you should expect in a patient with a normal creatinine clearance value. However in a patient with a creatinine clearance of only 10 ml/min the elimination rate constant will be quite different and if the same dosage regimen were used quite different plasma concentrations would be achieved (see Figure 16.8.1). The elimination rate constant for this patient would be 0.034 hr^{-1} ($t_{1/2} = 20 \text{ hr}$). Using the same dosing regimen:

$$\overline{C_p} = \frac{F \bullet Dose}{V \bullet k_{el} \bullet \tau} = \frac{1 \times 250}{13.3 \times 0.034 \times 6} = 92 \text{ mg/L}$$

This average plasma concentration is well above the maximum recommended value of 35 mg/L which should be avoided (in the PDR 89 p740). Clearly some dosage adjustment should be made to the dosage regimen.

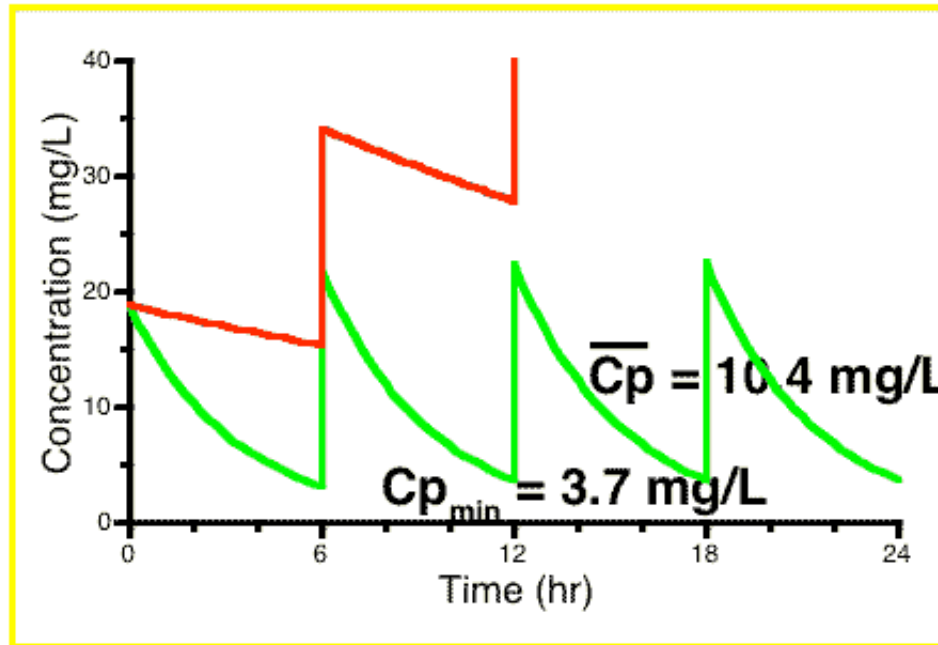


Figure 16.8.1 Linear Plot of C_p versus Time

We could consider

- a) changing the dose
- b) changing the dosing interval
- or c) changing both the dose and the dosing interval.

We can make these alterations easily using the $\overline{C_p}$ equation.

$$\overline{C_p} = \frac{F \bullet Dose}{V \bullet k_{el} \bullet \tau} = \frac{F \bullet Dose}{CL \bullet \tau}$$

Equation 16.8.2 Average Drug Concentration Equation

From this we can see that decreasing the dose or increasing the dosing interval will have the desired response.

Altered dose

Assuming that a C_p of 10.4 mg/L (the value obtained in the normal patient on a normal dosage regimen) is satisfactory we can calculate a dose to achieve this value as:

$$DOSE = \frac{\overline{C_p} \bullet V \bullet k_{el} \bullet \tau}{F} = \frac{10.4 \times 13.3 \times 0.034 \times 6}{1} = 28.2 \text{ mg (instead of 250 mg)}$$

Assuming $k_a \gg k_{el}$, $R = 0.815$ and $C_{pmin} = 9.3$ mg/L

Thus this new dosing regimen of 28 mg every 6 hours should work

Altered dose interval

$$\tau = \frac{\text{DOSE} \cdot F}{\overline{C_p} \cdot V \cdot k_{el}} = \frac{250 \times 1}{10.4 \times 13.3 \times 0.034} = 53 \text{ hours (instead of 6 hours)}$$

Therefore giving 250 mg every 53 hours should achieve a satisfactory plasma concentration profile.

$$R = 0.165; C_{pmin} = 3.7 \text{ mg/L}$$

We would expect greater fluctuations with this method and dosing every 53 hours is not all that convenient. Every 6 hours is not all that great either if a longer dosing interval would work. We might consider dosing every 24 hours.

Altered dose and interval

Using $t = 24$ hours

$$\text{DOSE} = \frac{\overline{C_p} \cdot V \cdot k_{el} \cdot \tau}{F} = \frac{10.4 \times 13.3 \times 0.034 \times 24}{1} = 113 \text{ mg every 24 hours (maybe 100 mg every 24 hours)}$$

$$R = 0.442; C_{pmin} = 6.7 \text{ mg/L}$$

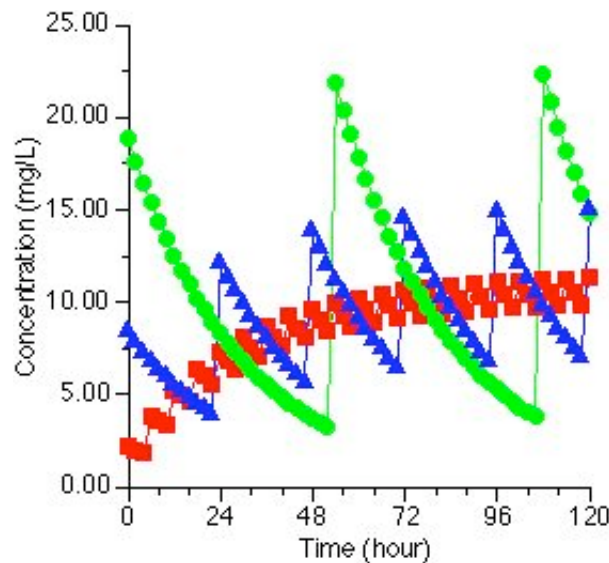


Figure 16.8.2 Plot of C_p versus Time

The lines in Figure 16.8.2 were calculated to achieve a $\overline{C_p}$ of 10.4 mg/L using 28 mg q6h, 250 mg q54h, or 113 mg q24h.

Calculator 16.8.1 Calculations Using the $C_{p_{average}}$ Equation 16.8.2

Drug Information		
Enter Drug Name	Kanamycin	
Enter required Cbar	<input type="text"/> mg/L	<input style="float: right;" type="button" value="?"/>
Enter required F	1 <input type="text"/>	
Enter Dose	250 <input type="text"/> mg	<input style="float: right;" type="button" value="?"/>
Enter V	13.3 <input type="text"/> L	
Enter kel	0.3 <input type="text"/> hr ⁻¹	
Enter tau	6 <input type="text"/> hr	<input style="float: right;" type="button" value="?"/>
<input type="button" value="Calculate missing Value"/>		

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$C_{p_{max}}/C_{p_{min}}$ Calculations

Another approach is to use the desired $C_{p_{max}}$ and $C_{p_{min}}$ to define the dosing regimen. The steps to be taken for this approach include:

a. Define $C_{p_{min}}/C_{p_{max}}$. From information on the drug with reference to the patient's clinical requirements. For example the normal upper limit for gentamicin peak concentrations might be 6 mg/L, however in case of life-threatening infection higher levels may be approached. Initial calculation might be based on a peak of 6 mg/L and a trough below 1 mg/L. (Use 1 mg/L as the trough and extend the interval when making the adjustment in τ .)

b. Determine CL_{Cr}. Probably from serum creatinine levels using the Cockcroft-Gault equation.

c. Determine kel. Using the equation $kel = km + b \cdot CL_{Cr}$ with km and b values from the literature

d. Calculate Tau. Since $\frac{C_{p_{min}}}{C_{p_{max}}} = R = e^{-kel \cdot \tau}$ and we know $C_{p_{min}}$, $C_{p_{max}}$, and kel we can calculate tau, τ . Typically this will be some uneven time value.

e. Round Tau. A more usual dosing interval should now be chosen. For example a tau of 7.8 or 6.7 hour could be rounded to 8 hours, thus dosing three times a day.

f. Recalculate R. A new value of tau results in a new value of R.

g. Calculate Maintenance Dose. The maintenance dose can be calculated from the minimum or the maximum plasma concentration. Thus

$$\text{Maintenance dose} = C_{p_{max}} \cdot V \cdot (1 - R) \text{ OR } = C_{p_{min}} \cdot V \cdot (1 - R)/R$$

h. Calculate Loading DOSE. The loading dose can be calculated directly (for an IV bolus) by equating C_p^0 and the $C_{p_{max}}$ value. Thus,

$$\text{Loading dose} = C_{p_{max}} \cdot V$$

Example:

A 75 kg, 65 year old male patient, serum creatinine concentration of 2.3 mg/100 ml, is to be given gentamicin IV to achieve a peak plasma concentration of 6 mg/L and trough concentration **below** 1 mg/L. The apparent volume of distribution is reported to be 0.28 L/kg. From Table 3-9 (Wagner, 1975 p161), km and b values are 0.02 and 0.0028, respectively.

a. $C_{p_{max}} = 6 \text{ mg/L}$ and $C_{p_{min}} = 1 \text{ mg/L}$

b. $CL_{Cr} = \frac{[140 - 65] \times 75}{72 \times 2.3} = 34 \text{ ml/min}$

c. $kel = km + b \cdot CL_{Cr} = 0.02 + 0.0028 \times 34 = 0.115 \text{ hr}^{-1}$

$$d. R = \frac{1}{6} = 0.1667 = e^{-0.115 \times \tau}$$

$$\ln(0.1667) = -1.792 = -0.115 \times \tau$$

$$\tau = 15.6 \text{ hour}$$

e. Since a longer dosing interval is needed to keep the trough level **below** 1 mg/L use a tau value of 18 hours.

$$f. \text{ New R value. } R = e^{-0.115 \times 18} = 0.1262$$

g. Calculate maintenance dose using $C_{p\max} = 6 \text{ mg/L}$ as reference point. Thus

$$\text{Maintenance dose} = C_{p\max} \cdot V \cdot (1 - R) = 6 \times 75 \times 0.28 \times (1 - 0.1262) = 110 \text{ mg}$$

Thus use 100 mg iv every 18 hours

$$C_{p\max} = \frac{\text{DOSE}}{V \cdot (1 - R)} = \frac{100}{75 \times 0.28 \times (1 - 0.1262)} = 5.45 \text{ mg/L}$$

$$C_{p\min} = C_{p\max} \cdot R = 5.45 \times 0.1262 = 0.69 \text{ mg/L}$$

h. The loading dose can be calculated as:-

$$\text{Loading dose} = C_{p\max} \cdot V = 6 \times 75 \times 0.28 = 126 \text{ mg. Using } 125 \text{ mg would give a } C_{p\max} = \frac{125}{75 \times 0.28} = 5.95 \text{ mg/L.}$$

Thus a loading dose of 125 mg followed by 100 mg every 18 hours should be satisfactory.

Comparison with PDR recommendation.

Usual dose for 75 kg patient is 75 mg q8h. With serum creatinine 2.3 mg/100 ml give 40 percent of 75 mg q8h. That is 30 mg q8h ($R = 0.399$) giving 2.38 and 0.95 for $C_{p\max}$ and $C_{p\min}$, respectively.

Calculator 16.9.1 Calculator Using $C_{p_{max}}$ and $C_{p_{min}}$ Criteria

Drug Information	<input type="button" value="Click for a new Problem or Enter your own Data"/>
Enter required $C_{p_{max}}$	6 mg/L
Enter required $C_{p_{min}}$	1 mg/L
Enter V	0.28 L/kg
Enter k_m or k_{nr} value	0.02 hr^{-1}
Enter Dettli slope value	0.0028 $min.ml^{-1}.hr^{-1}$
Patient Information	
Enter Patient Weight	75 kg
Age	65 years
Sex	<input checked="" type="radio"/> Male <input type="radio"/> Female
Enter Patient Serum Creatinine level	2.3 mg/100 ml
<input type="button" value="Calculate"/> CLcr, k_{el} and Tau	
Creatine Clearance	ml/min
Elimination Rate constant	hr^{-1}
R is	
Exact Tau	hr

Now enter a rounded value of Tau below

Enter Rounded Tau value	hr
<input type="button" value="Calculate"/> Maintenance and Loading Dose	
New R value	
Maintenance Dose	mg every hr
and Loading Dose	mg

Practice [calculating a patient's elimination rate constant](#) from creatinine clearance

References

- Wagner, J.G. 1975 **Fundamentals of Clinical Pharmacokinetics**, Drug Intelligence Publications, Inc., Hamilton, IL

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