

# CLEARANCE

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The concepts and terminologies of pharmacokinetics as used in *Australian Prescriber* articles may not be familiar to some readers who, like this author, were educated at a time when such matters were not discussed. Therefore, we plan to present a series of 'mini-articles' explaining the meaning and significance of important pharmacokinetic terms. The first three of these articles will deal with *clearance* and *distribution volume*, which are the two most important primary pharmacokinetic parameters, and *half-life*, which is the secondary parameter derived from them.

## What is clearance?

*Clearance* is the term that describes the efficiency of irreversible elimination of a drug from the body. Elimination in this context refers either to the excretion of the unchanged drug into urine, gut contents, expired air, etc., or to the metabolic conversion of the drug into a different chemical compound, usually in the liver but also in other organs. In the latter case, even though the metabolite is still in the body, the parent drug has been cleared or eliminated. Uptake of the drug into tissues is not clearance if the unchanged drug eventually comes back out of the tissue, however slowly this occurs.

*Clearance* is defined as 'the volume of blood cleared of drug per unit time' and the units are thus volume per time, usually litres per hour or mL per minute. We can refer to clearance by a particular organ, such as liver or kidney, by a particular metabolic pathway, or by the whole body. Total body clearance is the sum of all the different clearance processes occurring for a given drug.

Let's consider an example. What does it mean if the clearance of a particular drug by the liver is 1000 mL/min and liver blood flow is 1500 mL/min? It does not mean that 1000 mL of blood going through the liver is totally cleared of the drug and the next 500 mL is not cleared at all. Rather it does mean that two thirds (1000/1500) of the drug entering the liver in the blood is irreversibly removed by the liver (cleared) in one pass. The value of two thirds for this drug is called the *extraction ratio* and is simply one minus the ratio of concentration of drug in blood leaving the liver to that in blood entering the liver.

$$\text{extraction ratio} = 1 - \frac{\text{concentration out}}{\text{concentration in}} \quad \text{equation 1}$$

Obviously the most drug that could be removed by the liver is all that enters the organ. In this case the extraction ratio would be 1.0 and the hepatic clearance 1500 mL/min. The further significance of the extraction ratio will be discussed in a subsequent article.

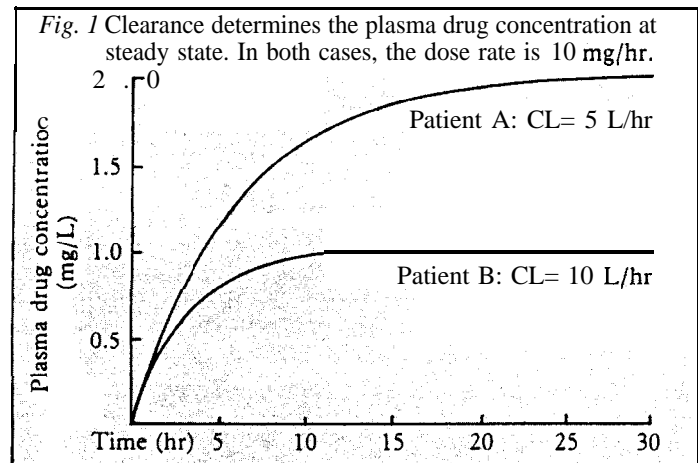
## Why is clearance important?

*Clearance* is the one parameter that determines the maintenance dose rate required to achieve a desired plasma

The formula for predicting the required dose rate is given by:

$$\text{maintenance dose rate (mg/hr)} = \frac{\text{desired blood drug concentration (mg/L)} \times \text{clearance (L/hr)}}{\text{equation 2}}$$

This is illustrated in Fig. 1 for constant rate intravenous infusion to two patients, in one of whom the clearance is double that of the other.



Note that, with a constant infusion, the blood concentration rises steadily until it eventually reaches a plateau or steady state. At this time the rate of drug administration equals the rate of drug elimination.

The oral dosing situation is slightly more complex because the drug concentration fluctuates during the dosing interval as drug is absorbed and eliminated. Eventually, however, the amount of drug eliminated during the dosing interval equals the dose administered, and the drug concentrations then fluctuate over the same range during each dosing interval i.e. steady state has been reached. At this point, the *average drug concentration over the dosing interval* is the same as the steady state plasma concentration for a constant intravenous infusion at the same dose rate. From equation 2 it is easy to see that, for a given dose rate, the blood drug concentration is inversely proportional to clearance e.g. if the clearance is reduced by half, the concentration will double (see Fig. 1).

## How is clearance measured?

The classical method of measuring renal clearance (e.g. of creatinine or drugs) is to measure the rate of excretion in urine and the blood concentration at the same time. This is the well-known  $CL = UV/P$  relationship where U is urine drug concentration, V is urine flow rate and P is the plasma (or blood) concentration.

To obtain *total body* clearance of a drug we can use equation 2

$$\text{clearance} = \frac{\text{dose rate}}{\text{steady state blood concentration}} \quad \text{equation 3}$$

Alternatively we can take frequent blood samples after a single intravenous dose, measure the drug concentration in each, and calculate the area under the drug concentration versus time curve (AUC) (see Fig. 2). Then

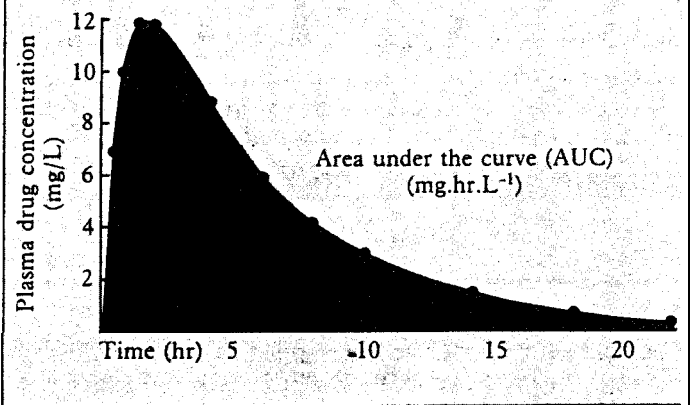
$$\text{clearance} = \frac{\text{dose}}{\text{AUC}} \quad \text{equation 4}$$

From this relationship, it can be seen that the total area under the blood concentration time curve after a single dose is, like the steady state concentration, only determined by the dose and the clearance.

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Clearance is the primary pharmacokinetic parameter that is a measure of the efficiency of drug elimination and therefore, for any given dose, determines the blood drug concentration and effect during constant dosing.

Fig. 2 Clearance can be determined by measuring plasma drug concentrations at multiple times after a single dose. Clearance (L.hr<sup>-1</sup>) = Dose (mg)/AUC (mg.hr.L<sup>-1</sup>).



# Letters

Letters, which may not necessarily be published in full, should be restricted to not more than 250 words. When relevant, comment on the letter is sought from the author. Due to production schedules, it is normally not possible to publish letters received in response to material appearing in a particular issue earlier than the second or third subsequent issue.

## Drug treatment of manic-depressive illness

Sir, — Dr Varghese has provided a very practical and comprehensive 'guide', to the drug treatment of manic depressive illness (Aust Prescr 1987;10:25-8).

I would like to make the following points:

1. Indomethacin is by no means the only non-steroidal anti-inflammatory drug to raise blood levels of lithium. Any of this group may, and usually, do so. It is imperative that this is recognised, as "the commonest cause of serum levels above the therapeutic range in my practice is the addition of a non-steroidal anti-inflammatory drug to the patient's medication by doctors who are aware that the patient is taking lithium, but unaware of the drug interaction. . .
2. In an era where patient education and informed consent are of paramount importance, patients being offered lithium should be provided with more than a card outlining the symptoms "of toxicity. The Melbourne Clinic has developed a very useful patient guide to lithium, and any interested practitioner can obtain a copy by writing to the Chairman, Drugs and Therapeutics Committee, The Melbourne Clinic, P.O. Box 194, Richmond 3121.

D. Grounds  
Psychiatrist  
Melbourne

**Dr Varghese comments:**

Dr Grounds raises some important issues in the treatment of affective disorder with lithium. My comments on the points raised are as follows:

1. My article does not imply that indomethacin is the only non-steroidal anti-inflammatory drug that can raise serum lithium. Other drugs in this group, including ibuprofen, phenylbutazone and naproxen can also potentially raise serum lithium.
2. I can only agree with Dr Grounds' statement regarding the education of the patient regarding lithium therapy. I have seen the Melbourne Clinic guide and do not hesitate to

recommend it. However, in addition, I prefer that my "patients have a" small card outlining the symptoms of toxicity because they can carry this around with them at all times.

## Cyanocobalamin

Sir, — The article *Time to drop cyanocobalamin* (Aust Prescr 1987;10:3) reprinted from Drug and Therapeutics Bulletin made an interesting and useful point. However, the supporting data given carries over a misquote in the Drug and Therapeutics Bulletin. This leads to an apparently illogical conclusion about the required dose of hydroxocobalamin. The statement is made that 30% of a 1000 microgram dose of hydroxocobalamin is retained (and presumably 70% of the dose is excreted), whereas the reference from which these figures were taken<sup>2</sup> states that 70% of a 1000 microgram dose of hydroxocobalamin is retained (and about 30% is excreted). The correctly quoted figure makes it more readily understandable why doses of hydroxocobalamin can be given at intervals as long as 10 months.

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**REFERENCE**

1. Anonymous. Time to drop cyanocobalamin? Drug Ther Bull 1984;22:43-4.
2. Chanarin I. The, megaloblastic anaemias. 2nd ed. Oxford: Blackwell Scientific Publications, 1979.

*The Editor comments:* " ~

My thanks to Ms Raymond for pointing out the error which illustrates the importance of checking primary references.