

List of proprietary names of drugs mentioned in article

acyclovir	Zovirax	trimethoprim/ sulphamethoxazole	Bactrim, Septrin, Resprim, Trib
fluorouracil	Efudix, Fluoroplex	trimethoprim	Alprim, Triprim
hepatitis B vaccine	Engerix-B, H-B-Vax II	pentamidine isethionate	Pentacarinat
zidovudine	Retrovir	nystatin	Mycostatin, Nilstat
ketoconazole	Nizoral	clotrimazole	Canesten, Gyne-Lotremin Vaginal, Clonea, Lotremim
metronidazole	Flagyl, Metrogyl, Metrozine, Protostat	miconazole	Daktarin, Gyno-Daktarin 7, Monistat Vaginal, Monistat-Derm
tinidazole	Fasigyn	econazole nitrate	Ecostatim, Pevaryl
benzyl benzoate	Ascabiol		
lindane	Quellada		

Pharmacokinetics made easy 6

PREDICTING DRUG INTERACTIONS AND THE EFFECTS OF DISEASE STATES FOR METABOLISED DRUGS

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For drugs which are cleared mainly by metabolism, we looked in Article 4 of this series at the physiological factors which determine systemic clearance (Aust Prescr 1990;13:88-9), and in Article 5 at factors which determine first pass clearance (Aust Prescr 1991;14:14-6). Drugs given orally are subject to both first pass clearance and systemic clearance. We now have to put these together and look at the physiological processes determining steady state concentrations of various types of drugs when they are given either orally or intravenously (systemically). For the moment, we will continue to assume that the drug is totally metabolised, and will then go on to see how knowledge of a few very simple pharmacokinetic parameters can allow rather wide-ranging predictions of how a drug will behave in practice.

1. What determines steady state drug concentrations during chronic dosing?

The first point to note is that it is generally the unbound drug (that not bound to plasma proteins or blood cells) which interacts with receptors and produces drug effects. We will therefore have to look at the factors determining both unbound and total steady state drug concentrations. Once again, the two limiting examples of high and low hepatic

clearance drugs will be considered. Table 1 summarises the factors involved. Fortunately, when all the equations are solved, the situation turns out to be very simple.

In all circumstances except one, the sole determinant of steady state unbound drug concentrations is the activity of the drug metabolizing enzymes in the liver (intrinsic clearance in pharmacokinetic terms). This applies to low clearance drugs given either orally or intravenously (systemic clearance is important here — see Article 4) and to high clearance drugs given orally (first pass clearance is of major importance here — see Article 5). It follows that circumstances which alter the drug metabolizing enzymes, such as co-administration of inducers or inhibitors, will alter steady state drug concentrations and effects. Circumstances which alter liver blood flow, such as cardiac failure, will usually be of less importance unless this also affects the activity of the drug metabolizing enzymes. It will be apparent from Table 1 that total but not unbound drug concentrations are affected by protein binding. The importance of protein binding — or perhaps the lack of importance — will be considered in a future article.

For those relatively few instances where high clearance drugs are given systemically for long enough to reach steady state,

Table 1

Physiologic parameters determining steady state concentration of highly metabolised drugs during chronic dosing.

For orally administered drugs, a combination of factors determining first pass clearance and systemic clearance (of the drug escaping first pass extraction) are involved. For intravenously administered drugs, only systemic clearance is important.

Type of drug and examples	Determinants of steady state blood concentration	
	Unbound concentration	Total concentration
Oral administration		
Low hepatic extraction	Intrinsic clearance	Intrinsic clearance and fraction unbound
High hepatic extraction	Intrinsic clearance	Intrinsic clearance and fraction unbound
Intravenous administration		
Low hepatic extraction	Intrinsic clearance	Intrinsic clearance and fraction unbound
High hepatic extraction	Hepatic blood flow and fraction unbound	Hepatic blood flow

Note that in all situations except one, the single physiological factor determining unbound (active) drug concentration during chronic dosing is intrinsic clearance (hepatic enzyme activity). Fraction unbound (protein binding) is a factor in total but not unbound drug concentration in these cases.

hepatic blood flow and protein binding are the determinants of unbound drug concentrations. With these drugs, virtually all the drug delivered to the liver is taken out each time, so the rate of delivery becomes the main factor. Protein binding becomes important because the higher the binding, the more can be 'held' in the blood for the presentation to and extraction by the liver. Examples of highly bound drugs are lignocaine given intravenously for arrhythmias or morphine given systemically for pain. Factors which alter liver blood flow, such as cardiac failure, exert major effects on steady state concentrations of such drugs.

2. How to determine the relative importance of metabolism predicted as follows: and renal excretion

So far we have been assuming that the drug is nearly completely metabolised. In fact, all drugs are partly metabolised and partly excreted unchanged by the kidney. The usual way to determine the relative importance of the two elimination mechanisms for a particular drug is to give a dose of the drug, collect all the urine, measure how much drug comes out unchanged (the rest is metabolised) and to express this as a fraction of the dose given. This is *the fraction excreted unchanged*, which can vary from close to 0 (nearly all the drug is metabolised e.g. propranolol, morphine, tolbutamide, theophylline) to close to 1 (nearly all the drug is excreted unchanged e.g. penicillin, amoxycillin, gentamicin, digoxin). It is apparent that *the fraction of the dose which is metabolised is* (1-fraction excreted unchanged).

3. Clearances are additive — calculating hepatic and renal clearances

The total body clearance is the sum of all the individual clearance processes occurring. As these are usually mainly renal clearance of unchanged drug and hepatic clearance by metabolism:

$$\text{total clearance} = \text{renal clearance} + \text{hepatic clearance} \quad \text{equation 1}$$

The fraction of drug excreted unchanged is then the fraction which renal clearance represents of total clearance:

$$\text{fraction excreted unchanged} = \frac{\text{renal clearance}}{\text{total clearance}} \quad \text{equation 2}$$

and the fraction metabolised is:

$$\text{fraction metabolised} = \frac{\text{hepatic clearance}}{\text{total clearance}} \quad \text{equation 3}$$

It follows from these relationships that knowing the total clearance and the fraction excreted unchanged, renal clearance can be calculated from equation 2 and then hepatic clearance from equation 1.

4. Predicting everything about a drug from a few simple pharmacokinetic parameters

Because pharmacokinetics is now described in terms of physiological processes, it is possible to predict how changes in these processes, due for example to drug interactions or disease states, will affect the handling of a drug by the body. This is illustrated in Table 2 for 3 different types of drugs. We will look at how it works for Drug A and you can complete the Table for Drugs B and C.

If total body clearance, volume of distribution and the fraction excreted unchanged are known, the rest can be calculated or

predicted as follows:

From Sections 2 and 3 above, the fraction of the dose of Drug A which is metabolised is 0.9 (1-0.1) and the hepatic clearance is therefore 72 L/hr (0.9 X 80). As liver blood

Table 2

Predicting how drugs will behave pharmacokinetically in various situations

	Drug A	Drug B	Drug C
known parameters			
Total clearance (L/hr)	80	3	7
Volume of distribution (L)	500	25	420
Fraction excreted unchanged	0.1	0.1	0.8
Liver blood flow (L/hr)	90	90	90
Predicted			
Renal clearance (L/hr)	8		
Hepatic clearance (L/hr)	72		
Hepatic extraction ratio	0.8		
Maximum oral bioavailability (%)	20		
Affected by induction/inhibition			
of liver enzymes when given orally		Yes/No	
Affected by liver blood flow			
- (e.g. cardiac failure) when given intravenously		Yes/No	
Decrease dose in liver disease		Yes/No	
Decrease dose in renal failure		Yes/No	
Half-life (hr)			
($0.693 \times \text{Volume of distribution}$)			
Clearance	4		
Likely dosing schedule (times per day)		6	
Time to reach steady state (hr)		20	

The completed information for Drug B and Drug C can be found on page 61.

flow is around 90 L/hr, the hepatic extraction ratio is 0.8 (72/90) (see Article 4). The fraction escaping first pass extraction is therefore 0.2 (1-0.8), so that the *maximum* oral bioavailability will be 20%. It might be even less if the drug is also poorly absorbed from the gut into the portal circulation (see Article 5).

The drug has a relatively high hepatic extraction ratio (0.8) so from Table 1 we can see the steady state drug concentration will be determined mainly by hepatic enzyme activity when given orally and by liver blood flow when given systemically. There will be decreases in both first pass clearance (increased oral bioavailability) and systemic clearance in liver disease so dose reduction will be mandatory. Only 10% is renally cleared (fraction excreted unchanged is 0.1) so dose reduction will not be necessary in renal failure unless there are active metabolites which are mainly renally cleared.

From the volume of distribution and the clearance, the half-life is calculated as 4 hours (see Article 3. Aust Prescr 1988;11:57-9). Dosing will thus need to be 4-6 times a day

unless a sustained release form is available. Steady state will be reached after about one day of treatment (3-5 half-lives — see Article 3).

Put briefly, when given pharmacokinetic information about a drug, as in product information, it is only necessary to ask the following questions to predict reasonably well what clinical situations are likely to require care or possible dose alterations due to a potential for changed pharmacokinetics:

- Is it mainly metabolised or mainly renally excreted?
- If metabolised, does it have high or low hepatic clearance?
- What is the half-life?
- Are there complicating factors such as active metabolites?

In the next article, we will see how similar predictions can be made for renally excreted drugs based on a knowledge of the processes by which they are excreted.

Abnormal laboratory results

DIABETES MONITORING; USE OF GLYCATED HAEMOGLOBIN AND GLYCATED PROTEIN ASSAYS

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SYNOPSIS

Both glycosylated hemoglobin and glycosylated serum protein assays are useful clinical indices of mean glycaemic control in diabetes management. Neither assay correlates perfectly with mean blood glucose levels and both are subject to error and artifact. It has been suggested that the assays are complementary and that both assays should be performed simultaneously to increase the reliability of the estimation of glycaemia. However, many experienced physicians are willing to rely on one or other assay providing that there is reasonable agreement with serial blood glucose levels determined either by the patient or a laboratory, but with the use of both assays when there is an unexplained discrepancy.

The phenomenon of glycation (or glycosylation) of proteins to form neoglycoproteins has long been recognised in the area of food technology as a cause of the 'browning reaction'. In recent years there has been an increasing understanding of the phenomenon of *in vivo* glycation of proteins, leading to the

development of assays which are indicators of mean glycaemic control in patients with diabetes. There has also been intensive study of the possibility that the phenomenon of protein glycation is a significant contributor to long-term diabetic complications — either by causing changes in structural proteins such as collagen, or by altering function of other proteins such as receptors, enzymes or the apolipoproteins of circulating lipids.

Measurements of circulating neoglycoproteins have been proposed as a marker of the exposure of circulating proteins to glucose and, by inference, a measure of the degree of glycaemic control. Assays of 3 different protein types have been used for monitoring blood glucose control in diabetes. Each assay reflects the life span of that protein in the circulation e.g. glycosylated hemoglobin (HbA_{1c}) indicates glycaemic control over about 3 months, the life of the red cell; glycosylated serum proteins or glycosylated serum albumin reflect glycaemic control over about 6 weeks, the life of serum albumin in the circulation. It should be noted that a