

Pharmacokinetics made easy 4.

HOW DRUGS ARE CLEARED BY THE LIVER

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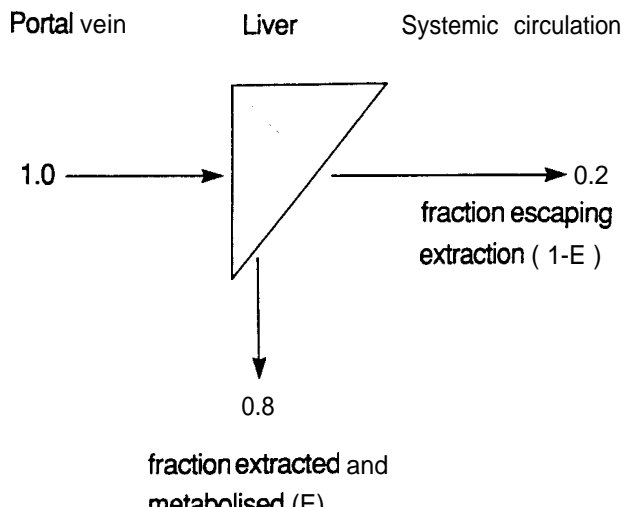
The two major routes of drug elimination from the body are excretion as unchanged drug by the kidneys and elimination by metabolism in the liver. The balance between these depends on the relative efficiency of the two processes. For the purposes of this article, we will assume that the only method of clearance is by liver metabolism (this is essentially the case for many drugs) and consider the physiological factors which determine this process, i.e. we are considering only **hepatic** clearance. In a later article, the factors determining renal drug clearance will be looked at.

1. How hepatic extraction ratio and systemic clearance are related

In the first article in the series (Clearance. Aust Prescr 1988;11: 12-13) we introduced the term 'hepatic extraction ratio', which is the fraction of the drug entering the liver in the blood which is irreversibly removed (extracted) during one pass of the blood through the liver. It is apparent that the extraction ratio could range from 0 (no drug at all is extracted) to 1.0 (all the drug entering the liver is extracted in one pass). This is illustrated in Fig. 1.

Fig. 1

Blood carrying drug enters the liver from the systemic circulation in the portal vein. In this example, the fraction extracted during each pass through the liver (E) is 0.8, so that 0.2 of the drug (1-E) survives to re-enter the systemic circulation from the hepatic vein. For a usual liver blood flow of 1500 mL/min, the clearance of this drug would be $0.8 \times 1500 = 1200$ mL/min.



It is intuitively obvious that clearance of drug by the liver will depend on the rate of delivery of drug to the liver (the hepatic blood flow) and on the efficiency of removal of drug which is presented to it (the extraction ratio). For example, consider the case of **propranolol** where 80% of the drug in the blood entering the liver is extracted in each pass (the extraction ratio is 0.8) and liver blood flow is 1500 mL/min. Then 0.8 of 1500 mL of blood is cleared of **propranolol** each minute, i.e. the hepatic clearance is 1200 mL/min.

Put more generally,

$$\text{hepatic clearance} = \text{hepatic blood flow} \times \text{hepatic extraction ratio} \quad \text{equation 1}$$

Thus, the two overall determinants of hepatic clearance are the efficiency of drug delivery in the blood (blood flow) and the efficiency of drug removal from the blood (extraction ratio). We now need to dissect further the extraction ratio term to see what determines how effectively the liver removes drug which is presented to it.

2. What determines hepatic extraction ratio

The equation describing the physiological parameters determining extraction ratio is as follows:

$$\text{extraction ratio} = \frac{(\text{unbound fraction} \times \text{intrinsic clearance})}{\text{blood flow} + (\text{unbound fraction} \times \text{intrinsic clearance})} \quad \text{equation 2}$$

Now let us consider what each of these terms means (we already know what hepatic blood flow is).

Unbound fraction: In some, but not all, circumstances the ability of the liver to remove drug depends on how tightly drug is bound to proteins and cells in the blood. In general, it is only free (unbound) drug which is available for diffusion from the blood into the liver cell where metabolism takes place. The exceptions, drugs which are very highly extracted by the liver, will be discussed below.

Intrinsic clearance: This is the intrinsic ability of the liver to remove (metabolise) drug in the *absence* of restrictions imposed on drug delivery to the liver cell by blood flow and protein binding. It is what hepatic clearance would be if hepatic blood flow was unlimited and all the drug were unbound. In biochemical terms, it is really a measure of how active the liver drug metabolizing enzymes are with that particular drug as substrate. Intrinsic clearance can be very high, in fact many times greater than hepatic blood flow, but it should be remembered that drug cannot be cleared more rapidly than it is presented to the liver, so that actual hepatic

3. Simplifying the situation

From equations 1 and 2 above, the full equation describing hepatic drug clearance is:

equation 3

$$\text{hepatic clearance} = \text{blood flow} \times \frac{(\text{unbound fraction} \times \text{intrinsic clearance})}{\text{blood flow} + (\text{unbound fraction} \times \text{intrinsic clearance})}$$

This is complicated, and it is difficult to visualise what a change in one of the parameters would do to hepatic clearance. We can simplify matters by considering two limiting cases, one where the liver enzymes have very low activity towards a drug, and a second where the enzymes have very high activity.

(i) *The very low enzyme activity case*

When the intrinsic clearance (enzyme activity) is much, much less than liver blood flow, equation 3 cancels out to become:

equation 4

$$\text{hepatic clearance} = \text{unbound fraction} \times \text{intrinsic clearance}$$

This is now a simple situation where we can say that clearance of such a drug by the liver depends directly on the degree of protein binding in the blood and the activity of the drug metabolizing enzymes towards that particular drug. It does *not* depend on liver blood flow. As the capacity of the liver to remove drug is very limited, the liver is taking out drug as quickly as it can, even at low rates of delivery (blood flow). Increasing or decreasing the rate of supply by increasing or decreasing liver blood flow therefore makes no difference to the actual clearance. Such drugs are called capacity limited, low hepatic clearance or low hepatic extraction ratio drugs. Diazepam is a good example.

(ii) *The very high enzyme activity case*

When the intrinsic clearance is much, much higher than liver blood flow, equation 3 cancels out to become:

equation 5

$$\text{hepatic clearance} = \text{liver blood flow}$$

The enzymes are so active that the liver removes all or nearly all the drug presented to it, so that the only thing determining the actual hepatic clearance is the rate of supply of drug to the liver (**hepatic blood flow**). As nearly all the drug is already being removed, changing the activity of the enzymes **will** make little or no difference. Even bound drug can be stripped off in one pass, so that protein binding also is not important. These drugs are called flow limited, high **hepatic** clearance or high hepatic extraction ratio drugs. **Glyceryl trinitrate** is a good example.

4. Practical application of these concepts

We are now in a position to put these concepts to use in relation to specific drugs which are cleared mainly by metabolism. Simply by classifying a drug as having low or high hepatic extraction and **therefore** clearance, we can know what factors determine its hepatic clearance and thus its plasma concentrations and effects during maintenance dosing. Fig. 2 shows the hepatic extraction **ratio** for a number of important drugs and summarises the physiological factors important in their hepatic clearance.

5. Systemic clearance and pre-systemic or first pass extraction

So far we have been dealing with systemic clearance, i.e. clearance of drugs from the systemic circulation. Orally administered drugs are absorbed from the gut lumen into the portal circulation and must pass through the liver before reaching the systemic circulation. **Pre-systemic** or first pass extraction refers to removal of drugs during this first pass through the liver during drug **absorption**. While the basic concepts are similar to those discussed in this article, there are important differences in the factors determining first pass extraction of high extraction ratio drugs. Drug absorption, **bioavailability** and first pass extraction **will** be discussed in the next article.

Fig. 2

Hepatic extraction ratio and hepatic clearance of some important drugs. The major determinants of **hepatic** clearance and steady state plasma concentrations during maintenance dosing are illustrated.

