

BIOAVAILABILITY AND FIRST PASS CLEARANCE

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1. Getting the definitions straight

As the terms absorption, first pass clearance, bioavailability and bioequivalence are often used loosely, we should first make sure of the definitions.

Absorption: is the extent to which intact drug is absorbed from the gut lumen into the portal circulation.

The factors affecting absorption are summarised in Table 1.

First pass clearance is the extent to which a drug is removed by the liver during its first passage in the portal blood through the liver to the systemic circulation.

This is also called first pass metabolism or first pass extraction.

Bioavailability: is the fraction of the dose which reaches the systemic circulation as intact drug.

It is apparent that bioavailability will depend both on how well

the drug is absorbed and how much escapes being removed by the liver before reaching the systemic circulation (Fig. 1).

bioavailability = fraction absorbed X (1 - extraction ratio) equation 1

where (1 - extraction ratio) is the fraction of drug escaping extraction by the liver. The fact that it is 1 - extraction ratio is important for bioavailability as will be seen below.

Bioequivalence: is a clinical definition referring to two formulations of a drug. Two formulations of the same drug are considered bioequivalent if the extents and rates of absorption of drug from them are so similar that there is likely to be no clinically important difference between their effects, either therapeutic or adverse.

The clinical decision as to what would be a clinically important difference will vary from drug to drug. For example, small differences between formulations may be important for drugs such as digoxin which have low therapeutic ratios, or for drugs such as phenytoin which have non-linear kinetics. A larger difference may be tolerated for drugs such as amoxicillin which have high therapeutic ratios.

Table 1

Determinants "of drug absorption from the gut

A. Dissolution

- physico-chemical properties of drug
- crystal size and form
- excipients
- special dosage forms (sustained release, enteric coated)
- pH (stomach and small intestine)

B. Gastric emptying rate

- stability of drug at acid pH
- solution or solid dosage forms (liquids and small particles empty more quickly)
- affected by: food; antacids; drugs (opiates, anticholinergics, metoclopramide); disease (autonomic neuropathy)

C. Intestinal motility

- dissolution of slowly soluble drugs (digoxin, sustained release formulations)
- chemical degradation or metabolism by microflora
- affected by: drugs (opiates, anticholinergics, metoclopramide); disease states (gastroenteritis)

D. Drug interactions in the gut lumen

- complexation (tetracycline with divalent metal ions)
- adsorption (anion exchange resins)
- food interactions (many antibiotics)

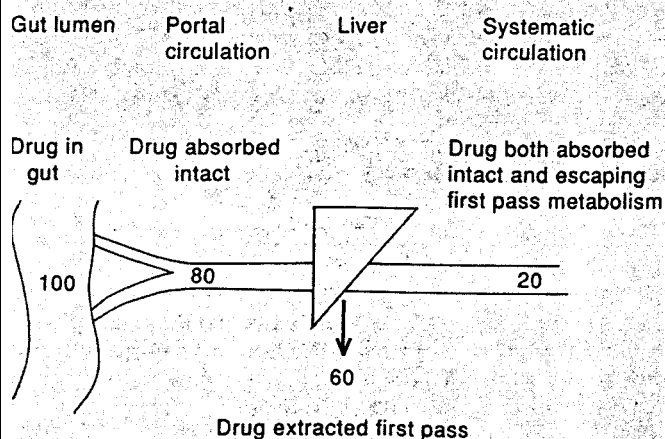
E. Presage through the gut wall

- physico-chemical characteristics of the drug (Quarternary ammonium compounds)
- metabolism by enzymes in the intestinal endothelium

Fig. 1

Factors affecting bioavailability.

In this example, 80 mg of the original 100 mg dose are absorbed intact into the portal circulation (fraction absorbed is 0.8). The hepatic extraction ratio is 0.75, so that 60 mg are extracted in the first pass through the liver and 20 mg escape extraction. The bioavailability (see equation 1) is fraction absorbed X (1 - extraction ratio) which is $0.8 \times (1 - 0.75) = 0.2$ (20%).



2. How is bioavailability measured?

Absolute bioavailability is measured against an intravenous reference dose (the bioavailability of an intravenous dose is 100% by definition). The usual method is to give a group of volunteers intravenous and oral doses of the drug on separate occasions. The areas under the plasma drug concentration versus time curves (AUC) after the two doses, are used to calculate the bioavailability of the oral formulation by simple proportion. For example, if the same intravenous and oral doses are given and the oral AUC is 50% of the intravenous AUC, the bioavailability of the oral formulation is 50%. The fact that the bioavailability is only 50% might be due to incomplete absorption, first pass clearance or a combination of these. Other methods which are used less frequently include comparing the urinary recoveries of drug or metabolize after intravenous and oral doses, or measuring the steady state plasma drug concentrations during intravenous and oral dosing.

The bioavailability of one oral formulation is often assessed against a second oral (reference) formulation. This is referred to as measuring relative bioavailability, and is commonly done for new generic products where the reference formulation is the innovator's brand or the market leader formulation (brand) for that drug. It is called relative bioavailability as drug from both products could be subject to first pass clearance and this would not be detected. This type of study provides a measure of the relative performance of two formulations in getting drug absorbed.

3. What determines first pass clearance?

Let us now concentrate on first pass clearance and, for the moment, assume that all the drug is absorbed intact from the gut lumen into the portal circulation. The bioavailability then depends only on the fraction escaping first pass hepatic extraction as the fraction absorbed is 1.0 (see equation 1), Then,

bioavailability = (1 - hepatic extraction ratio) equation 2

The determinants of hepatic extraction ratio were considered in detail in the previous article (*How drugs are cleared by the liver*. Aust Prescr 1990; 13:88-9). Let us take the same two limiting cases as previously, and look at the effects on bioavailability of increasing or decreasing the hepatic extraction ratio by changing the activity of the liver drug metabolizing enzymes. Table 2 summarises these effects.

Low hepatic extraction ratio drugs

In the case of drugs such as theophylline which are poorly extracted by the liver, nearly all the dose gets through the liver first pass and bioavailability is essentially complete as long as they are well absorbed from the gut. Even doubling or halving the minor proportion extracted by the liver does not make any significant difference to bioavailability (see Table 2).

High hepatic extraction ratio drugs

For drugs such as verapamil which are efficiency extracted by the liver, most of the dose is extracted on the first pass through the liver so that only a minor proportion reaches the systemic circulation intact (Table 2). Inducing or inhibiting the metabolizing enzymes has only a small effect on hepatic extraction ratio, and thus on systemic clearance (See previous article Aust p_e, 1990; 13:88-9), but has a major effect on the proportion escaping extraction (which is 1- extraction ratio), and thus has a major effect on bioavailability (Table 2).

Thus for these drugs, hepatic enzyme activity is the major determinant of first pass metabolism and oral bioavailability, whereas hepatic blood flow is the major determinant of systemic clearance.

4. Why is first pass clearance important?

- (i) *Variability in drug response.* As seen from Table 2, even small changes in the extraction of drugs such as verapamil can cause large changes in bioavailability. Thus the plasma concentrations of such drugs after oral administration are more variable, both within and between individuals, than the plasma concentrations of drugs with close to complete bioavailability.
- (ii) *Relationship between oral and intravenous doses.* In example B in Table 2, only 10% of the oral dose reaches the systemic circulation as against, by definition, 100% of an intravenous dose. If there are no other complicating factors, the oral dose will therefore have to be 10 times the intravenous dose to achieve similar plasma concentrations and effects by the two routes of administration. For drugs with complete bioavailability, oral and intravenous doses are similar.
- (iii) *Alternative routes of administration.* Some drugs are so highly extracted by the liver that their oral bioavailability is negligible. Glycerol trinitrate and ergotamine are examples, both having first pass clearances of 99% or more and therefore oral bioavailabilities of less than 1 % of the dose. Glycerol trinitrate is administered by the sublingual route because the venous drainage from the mouth goes directly to the systemic circulation and first pass clearance by the liver is avoided. Percutaneous or transdermal administration of glycerol trinitrate achieves the same result and also provides a slow, sustained delivery of drug.

Part of the rectal circulation is systemic rather than portal, so rectal administration reduces first pass clearance. However, absorption of drugs from the rectum is often erratic and incomplete.

Administration by inhalation can also be used for systemic

Table 2
Effects of increase or decrease in hepatic drug metabolising enzyme activity on bioavailability

Hepatic enzyme activity	% extracted first pass	Bioavailability (% escaping first pass extraction)
A. Low extraction ratio drug		
Normal	2	98
Doubled (induced)	4	96
Halved (inhibited)	1	99
B. High extraction ratio drug		
Normal	90	10
Doubled (induced)	95	5
Halved (inhibited)	83	17

All the dose is assumed to be absorbed intact from the gut lumen. The low extraction ratio example is characteristic of theophylline which has an intrinsic clearance (see previous article Aust Prescr 1990;13:88-9) of about 15 mL/min. The high extraction ratio example is characteristic of verapamil which has an intrinsic clearance of about 15 000 mL/min. Liver blood flow is normally around 1500 mL/min.

delivery without first pass clearance of some drugs (e.g. ergotamine). When drugs are used by inhalation for local effects on the lung, extensive first pass clearance can be a protective mechanism against systemic effects of the drug which is swallowed (often as much as 90% of the inhaled dose) rather than passing to the lungs. Examples are the beta-2 receptor agonist **salbutamol** and the inhaled corticosteroid **beclomethasone**.

- (iv) **Drug integrations.** As seen in Table 2, induction or inhibition of drug metabolizing enzymes in the liver by other drugs or environmental agents such as cigarette smoke can cause large changes in the **bioavailability** of high, but not low, clearance drugs. An example of this effect is shown in Fig. 2.

- (v) **Liver disease.** In chronic liver disease, a substantial part of the portal circulation does not perfuse functional liver cells due to the presence of **intrahepatic** functional shunts or extrahepatic anatomic shunts. If 50% of the portal blood does not perfuse functioning liver cells, then 50% of first pass clearance will be avoided and bioavailability increased markedly. In example B in Table 2, **bioavailability** and effective dose would be increased from 10% to 55% (i.e. 5.5-fold) in this situation. **Thus, high hepatic extraction drugs given to patients with liver disease are particularly liable to overdosing and causing an increased incidence of adverse effects.**

Fig. 2

Effect on felodipine bioavailability due to a drug interaction with anticonvulsants.

▲▲ healthy control subjects; ●● epileptic patients on liver enzyme inducing anticonvulsants. The relative **oral bioavailability** in epileptic patients was reduced to 6.6% of that in healthy control subjects. As the usual absolute oral **bioavailability** of felodipine (compared to an intravenous dose) is about 15%, only about 1% of an oral dose would be absorbed

intact in patients on enzyme inducing anticonvulsants. In this study, 10 out of 12 control subjects, but none of the epileptic patients, experienced **vasodilator** adverse effects. In 4 of the 10 epileptic patients, **felodipine** could not be detected in plasma.

Adapted with permission from *Lancet* 1988;2:481.

