The liver is the main organ responsible for the metabolism of xenobiotics, including drugs. In liver disease, handling of drugs by the liver may be disturbed greatly by several mechanisms, including, principally, altered absorption, disposition (elimination) and distribution. The effect of drugs may be altered also in patients with hepatic dysfunction. It has been recognized for many years that some patients with liver disease are especially sensitive to the effects of some drugs, in particular sedatives such as benzodiazepines. This would appear to be a result of altered pharmacological responsiveness, rather than derangement of pharmacokinetics [1].

Absorption of drugs and distribution within the body may be disturbed in liver disease, leading to abnormal bioavailability. For example, the absorption of the beta blocker bisoprolol appears to be reduced in patients with advanced liver disease so that, although metabolism is impaired also, blood concentrations do not increase as much as expected [2]. Because of associated hypoalbuminaemia, drug binding may be reduced in liver disease, increasing the proportion of free drug available for metabolism; this also tends to normalize pharmacokinetics in patients with reduced metabolic capacity [3]. Reduced plasma protein binding also influences penetration of drugs into tissues and drug distribution. Obviously, the increased total body water found in liver disease, particularly in those with ascites, increases the volume of distribution of hydrophilic substances. In cholestatic liver disease, reduced bile acids in the intestine may impair drug absorption, and protein binding of drugs may be influenced by increases in the concentrations of bilirubin and bile acids in plasma, again affecting drug distribution and metabolism. Increased intrahepatic bile acid concentrations may also affect drug metabolizing enzymes [4].

The dominant factor affecting drug pharmacokinetics in patients with liver disease is abnormal drug disposition, and a study in this issue of the Journal by Bower and colleagues [5] illustrates well some of the complexities affecting drug disposition. They found that the aetiology of hepatic disease affected the disposition of alfentanil. Although some of this difference may have been caused by slightly more severe disease in patients with alcoholic liver disease, differences in drug disposition would be expected to vary with liver pathology, as discussed below.

Drug disposition is influenced by many factors in patients with liver disease, the most important of which are abnormal (usually reduced) liver blood flow, porto-systemic shunting and impaired metabolic capacity. These factors vary from patient to patient and their importance varies from drug to drug. Classically, drugs may be classified into three main groups with reference to hepatic metabolism: “high risk”, “limited risk” and “low risk” drugs [6]. The degree of risk depends largely upon the dependence of drug metabolism on liver blood flow. High risk drugs such as glyceryl trinitrate [7], propranolol [8], chlormethiazole [9] and pentazocine [10] have a high hepatic extraction—normally more than 60% of available drug in a single pass. The disposition of such drugs after oral administration is highly dependent upon liver blood flow, with first-pass elimination limiting systemic availability of absorbed drug. In patients with liver disease, liver blood flow is generally, although not invariably, reduced (again depending upon aetiology) and porto-systemic shunting allows blood draining from the splanchnic circulation to bypass the liver. Both of these factors may have a profound effect on drug pharmacokinetics, leading to high peak drug concentrations with less effect on drug half-life [6]. If such high risk drugs are to be prescribed in patients with liver disease, the dose to be administered should be reduced, rather than the frequency. The pharmacokinetic profiles of high extraction drugs after parenteral administration (which reduces the effect of high first-pass extract by allowing drug access to the systemic circulation without passing through the portal vein) might be expected to be relatively unchanged in patients with hepatic disease. In reality, factors such as decreased hepatic uptake of drugs and intrahepatic shunting complicate the situation [11].

Drugs which have an extraction of less than 30% in a single pass through the liver depend much less on liver blood flow and more on the metabolic capacity of the liver. Systemic bioavailability of these agents is much greater than for the high extraction drugs. Low extraction or limited risk drugs include chloramphenicol [12], theophylline [13] and outdated agents such as antipyrine [14] and aminopyrine [15], the clearances of which are now used as dynamic liver function tests. Caffeine is also a limited risk drug [16] and has been used recently in clearance studies to assess liver function. Although several sedatives, including diazepam [14] and phenobarbitone [17], are low extraction drugs, they should perhaps not be considered limited risk agents, as patients with liver disease show increased end-organ sensitivity.

Low extraction drugs, although dependent on the metabolic capacity of the liver rather than its blood flow, may demonstrate differences in metabolism in patients with liver disease because of the metabolic pathways involved. Oxidation of drugs (a phase I reaction) is carried out principally by the cytochrome P450 enzymes, which are situated predominantly in zone 3 (centrilobular area) of the hepatic lobule.
In contrast, enzymes responsible for conjugation (phase II reactions), such as the glucuronon transferases, are plentiful in zone 1 (the periportal area). Enzymes situated in zone 3, an area more prone to hypoxia, appear to be affected more in liver disease than those in zone 1 and there is some evidence that glucuronidation, a phase II reaction, is relatively well preserved in patients with liver disease, unlike phase I reactions [19]. In patients with some liver diseases, for example those caused by ethanol, enzyme induction may be present and influence drug metabolism. It is clear, therefore, that the "metabolic capacity" of the liver is not a homogeneous entity in patients with liver disease, but depends upon the metabolic pathways involved. For example, the pharmacokinetics of drugs such as lorazepam and morphine appear to be relatively normal in patients with liver disease, even though they are metabolized within the liver (because they undergo glucuronidation). Despite this, however, increased end-organ sensitivity to these drugs should place them within the "limited" rather than the "low risk" group, despite their pharmacokinetic profiles.

The pharmacokinetic profiles of low extraction drugs tend not to show particularly high peak blood concentrations, but rather increased half-life. Theoretically, it should be the frequency of drug administration that should be reduced, rather than the dosage.

It should be remembered that, whilst impaired hepatic drug disposition tends to prolong or increase the effect of many drugs, prodrugs, which commonly are activated by the liver to active compounds, may be handled abnormally [20] and have less effect.

The disposition of some drugs is relatively unchanged in patients with severe liver disease, for various reasons: for example, penicillins are eliminated principally by the kidneys, whilst other agents such as digoxin and phenytoin, although metabolized by the liver, have increased concentrations of free drug available for metabolism because of reduced protein binding [6]. Relatively preserved glucuronidation in liver disease mitigates against abnormal metabolism of some drugs, as discussed above.

The mechanism whereby normal disposition of some drugs occurs in patients with liver disease remains unclear. Whatever the reason for normal disposition in liver disease, such drugs may be considered low risk substances; these include cimetidine [21], digoxin [22], spironolactone [23] and frusamide [24]. Where possible, drugs in this group are the agents of choice for patients with liver disease, although again such factors as altered end-organ sensitivity, drug distribution or absorption and route of administration may influence their therapeutic effect.

In conclusion, drug handling in patients with liver disease is complex and involves many factors. Drug disposition depends upon such properties as the degree of first pass hepatic extraction and the enzymes involved in metabolism. Despite the theoretical rationale behind the pharmacokinetic changes predicted for various classes of drugs, individual variations in drug disposition in patients with liver disease makes monitoring of the patient's drug response and plasma drug concentrations (where possible) prudent. Even when disposition is unaffected, other factors, including increased patient sensitivity to the drug, need to be considered.

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REFERENCES


