What pharmacokinetic and pharmacodynamics factors need to be considered when prescribing drugs for patients with liver disease?

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Background

The liver has a key role in the metabolism and excretion of drugs. Liver dysfunction may influence drug pharmacokinetics and pharmacodynamics, with the nature and severity of the liver disease determining the clinical relevance of these changes (1-6). Unlike renal impairment, there is no endogenous marker in the body that can be used to predict the effect of liver dysfunction on excretion, and consequently be used as a guide for drug dosing. Therefore it is sometimes necessary to work from the principles below, to try and predict the pharmacokinetic changes that may occur in a patient with a specific type of liver disease. The extent of these changes is frequently complex, unpredictable and drug specific; as a result, estimates of dose reductions are difficult (1,2,4-7). The preferred approach to establishing how to use a drug in patients with liver disease is to perform a literature search to identify clinical studies or published guidance. As long as the type of liver disease matches that of the patient in question, this may provide more accurate information relating to actual pharmacokinetic changes and dose adjustments than using the principles discussed below, which provide only theoretical information (1). It is, however, important that the liver dysfunction in the study population is described in sufficient detail (i.e. type and severity) to determine whether it can be applied to the patient in question; descriptions such as 'mild' or 'severe' liver disease are inadequate. In addition to pharmacokinetic changes, patients with liver disease may also experience an altered response to the effects of some drugs (1-7).

Answer

General Considerations

In order to determine the suitability of a drug in a patient with liver disease, it is important to have a detailed knowledge of the pharmacokinetic and adverse effect profile of the drug, and the way in which the patient's liver disease may have altered drug handling (1,3,6). It is critical therefore to find out as much as possible about the patient's liver disease and overall medical condition. This Q&A will look at the pharmacokinetic and pharmacodynamic issues only. The relevance of a drug's adverse effects will be discussed in the linked Medicines Q&A.

In the absence of data in patients with liver disease, the following pharmacokinetic information in healthy subjects may help to predict changes in pharmacokinetics seen in patients with various types of liver dysfunction (2,3,6). Certain types of liver dysfunction (e.g. decompensated cirrhosis) may affect several pharmacokinetic parameters, therefore the choice of drug becomes more difficult and the patient's response more unpredictable.

Pharmacokinetics

Absorption:

- Is the drug lipid-soluble? Lipid-soluble drugs may be reliant on the action of bile salts to aid their absorption. These drugs may be less well absorbed in a patient with cholestasis, potentially leading to reduced plasma concentrations and reduced efficacy (1,8).

- The absorption of some drugs (e.g. furosemide) is delayed in patients with cirrhosis and ascites. This is not generally predictable simply by looking at pharmacokinetic data in healthy individuals (1,3).

Distribution:

- Is the drug water-soluble? If so it may distribute into the ascitic fluid, which may reduce concentrations of the drug achieved in other areas of the body, including its site of action. Larger loading doses may therefore be required (1-3,6).
- Is the drug highly protein-bound? Chronic liver disease may result in low albumin levels. Highly protein-bound drugs are affected by hypoalbuminaemia, which causes the proportion of unbound drug to increase. This may result in increased adverse effects (1-3,6,7). Some drugs with high protein binding can be displaced from their binding sites by bilirubin in the presence of hyperbilirubinaemia, again leading to a higher than normal concentration of free drug (2).

Metabolism:

- Is the drug metabolised by the liver? Reduced hepatic metabolism of drugs is likely to be most significant in patients with decompensated cirrhosis, acute liver failure and cholestasis. Reduced hepatic cell mass due to cirrhosis may lead to a subsequent reduction in drug metabolising enzymes, accumulation of active drug and the potential for an enhanced response and increased adverse effects. If metabolites are also active, this will complicate the picture and it may be impossible to predict the outcome. It is thought that CYP450-mediated phase I reactions are more likely to be affected than conjugation reactions such as glucuronidation; however there is evidence to suggest that glucuronidation reactions may also be impaired in some patients (1-7). Cholestasis results in an accumulation of bile acids (BAs) in the liver and in order to limit further hepatic exposure to them, adaptations within the liver occur. These include decreased expression of enzymes which produce bile acids, such as CYP7A1. There is also decreased expression of transporters, such as the OATP family members, which work to decrease the entry of bile acids into hepatocytes and also induction of transporters, such as the multidrug-associated resistance proteins (MRP) family members, which enhance excretion of BAs. The cumulative effect of these changes may decrease hepatic exposure to drugs but increase systemic and renal exposure. (9)
- Does the drug undergo high first-pass metabolism (i.e. does it have a high extraction ratio)? This is important in patients with advanced cirrhosis. In these patients, the reorganisation of the liver architecture may result in portal hypertension, which can lead to the development of a collateral circulation (varices) between the portal and venous system. If the drug undergoes substantial first-pass metabolism, this can result in a greater proportion of absorbed oral drug entering the systemic system, causing a large rise in bioavailability and the potential for increased adverse and therapeutic effects (1-4,6,8). Bioavailability information may help to identify whether a drug undergoes first-pass metabolism, i.e. if the bioavailability is high, there will be little pre-systemic (first pass) metabolism. Unfortunately the converse is not true, since low bioavailability may be due to other causes such as poor oral absorption (3).
- Impaired metabolic capacity is often indicated by an elevated INR (international normalised ratio), reduced albumin and/or encephalopathy. These patients may require reduced maintenance doses of hepatically metabolised drugs. Patients with portal hypertension and varices taking drugs with a high first pass metabolism may require reduced initial doses if given orally, as well as reduced maintenance doses. The extent of dose reduction is not generally predictable (1-3,6).

- Is the drug a pro-drug requiring activation in the liver? Poor liver metabolism may reduce the rate or extent of activation and reduce the therapeutic effect of these drugs. However, the activated drug may itself be metabolised in the liver or excreted via the biliary route and changes in the liver function may therefore reduce the rate or extent of excretion. The overall impact on the drug's pharmacological activity and whether dose adjustments are required is likely to be difficult to predict (5,7).

Excretion:

- Does the drug undergo biliary excretion? In cholestatic patients, elimination via the biliary route may be reduced, resulting in accumulation. This may be clinically relevant for drugs or metabolites that are active and that normally undergo significant biliary excretion (1-3,7,8).
- Does the drug undergo enterohepatic recirculation? If so, cholestasis may affect this phenomenon (1,3). Although there may be less recirculation in these patients, the drug may be excreted more slowly than usual, and predictions of outcomes are likely to be difficult.
- Is the drug or its active metabolite(s) renally excreted? Renal excretion of drugs may be affected in patients with liver disease. In cirrhotic patients, the creatinine clearance may overestimate the glomerular filtration rate, and if active drug or active/toxic metabolite is excreted via this route, dose reduction may need to be considered (1-3,6,7). In addition, some patients may have hepatorenal syndrome necessitating dose reduction (2,3,6,7). For certain drugs e.g. torasemide, renal excretion may increase to compensate for impaired hepatic metabolism (3).

The above highlights that it is possible for drugs to accumulate or show an increased risk of adverse effects in patients with liver disease, particularly those with advanced cirrhosis (2,3,6). Regardless of the aetiology of the liver disease, the liver appears to produce a hepato-protective response through alterations in ADME genes. These often lead to functional disturbances and decreased biliary elimination which may have significant implications in drug therapy (9). For this reason, drugs with shorter half-lives are generally preferred; and avoiding prolonged release preparations. Certain therapies may also be preferred if there is the potential to reverse the toxic effects of the drug quickly should accumulation occur. Drugs with a narrow therapeutic index should be used with caution (2,3,6).

Pharmacodynamics

Patients with cirrhosis or acute liver failure may be more sensitive to some of the pharmacological actions of drugs, including both therapeutic and adverse effects. Common examples include increased sensitivity to drugs acting on the central nervous system, and increased sensitivity to the renal side effects of non-steroidal anti-inflammatory drugs (NSAIDs). These patients may also experience a reduced response to some drugs (e.g. diuretics) (2-7).

Summary

Changes in liver function can affect the body's response to drugs due to both pharmacokinetic and pharmacodynamic changes. These changes can lead to a number of outcomes including reduced or enhanced therapeutic effects and/or excessive side effects. Multiple factors need to be considered when determining how the drug handling will be altered by the liver condition, and whether alternative therapies or dosage changes are required to maintain efficacy and avoid toxicity (1-7).

Pharmacokinetic changes can be complex and sometimes unpredictable. Different types of liver disease can affect a drug's kinetics in different ways and therefore it is difficult to give general advice. Clinical studies can sometimes be located that detail an accurate picture of how the handling of a specific drug has been altered in certain liver conditions, and from this, information may be available regarding adjustment of dosage. However, this is generally not the case, and a clinical decision may need to be made regarding choice of therapy and dosages employed. In the absence of clinical studies, it may be necessary to use pharmacokinetic information from healthy individuals to try and predict the effect the patient's liver disease may have on drug handling. It is helpful to identify the following pharmacokinetic parameters for the drug in question; liver disease can affect some or all of these and doses may need adjusting accordingly (1-3,5-7).

- Solubility of oral form - lipid or water-soluble? (may affect extent of absorption and distribution)
- Bioavailability - may help to identify drugs with a high first pass metabolism
- Distribution - into ascites?
- Protein binding - high or low?
- Metabolism - hepatic or other type of metabolism; prodrug; active or inactive metabolites; high first pass metabolism (or extraction ratio)?
- Excretion - renal or biliary, enterohepatic recycling?
- Half-life

Patients with cirrhosis or acute liver failure may also experience altered sensitivity to the pharmacological actions of drugs, particularly enhanced CNS effects, enhanced renal side effects with NSAIDs, and reduced sensitivity to some diuretics (1-7).

As well as taking pharmacokinetic and pharmacodynamic changes into account, it is also important to consider the side effect profile of a drug and patient-specific factors such as age, co-morbidities etc. The consequences of adverse effect profiles on liver disease are discussed in Medicine Q&A 171.3.

Limitations

Published literature, giving dosing advice, based on clinical studies in patients with liver disease should generally be used in preference to predictions made from pharmacokinetic parameters in healthy subjects. However it is important that the type and severity of liver disease in the study patients closely matches that of the patient in question, and that the study uses a dosing regimen that matches the one being used in practice,

The use of some medicines in patients with liver disease may be contra-indicated by the manufacturer. Use of the therapy would therefore be unlicensed.

References

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Quality Assurance

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Search strategy
Original search

- Embase: [exp LIVER DISEASE or exp BILIARY TRACT DISEASE] and [exp PHARMACOKINETICS or exp DRUG ADMINISTRATION] [Limit to: Publication Year 2005-2011 and Priority Journals and English Language and (Publication Types Review)]
- Medline: [exp LIVER DISEASES or exp BILIARY TRACT DISEASES] and [exp PHARMACOKINETICS or exp DRUG ADMINISTRATION SCHEDULE] [Limit to: Review Articles and English Language]
- NeLM search: liver disease
- NHS Evidence search: pharmacokinetics “liver disease”, limit to ‘evidence summaries’
- Pharmline: ["Liver Diseases" or "Liver Function-impaired") and ("Pharmacokinetics" or "Drug Administration Schedule"] [Limit by year: 2000-2009]
- Clinical expert: Penny North-Lewis, Lead Paediatric Liver Pharmacist, Leeds Teaching Hospitals NHS Trust, Leeds.
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Repeat search

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