Why is the adverse effect profile of a drug relevant when prescribing for patients with liver disease?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals

Date prepared: 30th October 2020

Background

In patients with liver disease, choosing the most appropriate drug to use and calculating the optimum dose can be complex and challenging. Liver dysfunction can affect the pharmacokinetics of a drug, but there are other factors to consider. The complications associated with some types of liver disease can increase the significance and risk of certain medication-related side effects. In addition, pharmacodynamic changes may cause a patient to be more susceptible to both therapeutic and adverse effects through, for example, heightened receptor sensitivity (1). This Medicines Q&A summarises the importance of adverse effect profiles in patients with liver dysfunction. Pharmacokinetic and pharmacodynamic considerations are discussed in Medicines Q&A - What pharmacokinetic and pharmacodynamic factors need to be considered when prescribing drugs for patients with liver disease?

Answer

The nature and severity of the liver disease in a specific patient will determine the clinical relevance of the adverse effect profile of a drug. It is therefore important to have a thorough understanding of a patient's liver condition (i.e. through knowledge of laboratory, scan and biopsy results and any signs/symptoms of liver disease), before the side effects of drug therapy are considered. The majority of patients have a pattern of liver dysfunction that falls within at least one of the categories described below. Overlap between these categories, and progression from one to another is common; patients should not be inappropriately compartmentalised (1). The information below describes the types of adverse effects that may be detrimental in patients with:

Any form of liver disease

The risk of drug-induced hepatotoxicity should be considered in all patients with liver dysfunction. It is beyond the scope of this Q&A to discuss hepatotoxicity in detail (more information can be found in references 2,3,5-8). However it is helpful to recognise that, as with other adverse effects, hepatotoxicity can be classed as intrinsic (predictable, reproducible and dose-dependent), or idiosyncratic (unpredictable and independent of dose) (2,4-7). It may be possible to reduce the incidence of intrinsic reactions by dose adjustment, however the majority of liver adverse effects are idiosyncratic (exceptions include paracetamol and methotrexate) (4,5). The decision to use or avoid a potential hepatotoxin will depend on the clinical urgency for treatment, the availability of safer alternatives, the length of treatment required, the incidence, severity, reversibility and type of drug-induced hepatic injury, and the nature, severity and stability of the patient's pre-existing liver disease (1,9).

There are a growing number of trials studying the use of hepatotoxic drugs in patients with chronic, underlying liver disease, a number of which support the safe use of some agents, despite contra-indications in the licensing information (9). In general, patients with pre-existing liver disease are thought to be at no greater risk of drug-induced liver damage than the general population, although there are a few exceptions (e.g.methotrexate, rifampicin) (1-4,6,9). Patients who already have liver problems, however, may have less hepatic reserve to enable them to cope should hepatotoxicity occur, and therefore it may be wise to avoid drugs that have a high incidence of causing liver damage (1,5,6,9). Drugs that rarely cause liver damage can often be used with caution (5).

Some drugs can cause mild, sometimes transient, clinically insignificant rises in LFTs. Although these drugs may not be hepatotoxic *per se*, the risks and benefits of using them in patients with liver disease should be carefully considered. Any changes in LFTs may skew the monitoring of the pre-existing liver condition, particularly if the LFTs are unstable prior to starting the treatment (5).

The prescribing of any drug that potentially affects liver function requires careful monitoring of the patient. It is helpful to be aware of the temporal relationship between the initiation of drug treatment and the expected effects on the liver (e.g. cholestatic, hepatocellular, mixed picture) (5,6,7). This may help to provide guidance on the frequency and duration of LFT monitoring, in order to identify problems early on. Some authors question the benefit of routine LFT monitoring for certain drugs because although transaminases may rise to more than three times the upper limit of normal, only a minority of these patients will go on to develop significant liver damage. In addition, for some drugs, the deterioration in liver function may be so sudden that routine monitoring fails to pick it up until it is too late (5,6,7).

In many patients, the risk of drug-induced hepatotoxicity is minimal, compared to the risk of other drug-related side effects (1). The following information is not exhaustive, but describes some of the most important adverse effect profile considerations in specific types of patients. As with hepatotoxicity, it may be possible to minimise any intrinsic adverse effects through dose reduction (4).

Cholestasis

- Pruritus - patients with cholestatic conditions often experience intense itching (1,10-12). This may be further aggravated by drugs that can cause urticaria or pruritus. It is therefore preferable to avoid drugs with a high incidence of these side effects (1,11).
- Fatigue – is one of the most common symptoms of chronic cholestatic conditions, significantly affecting quality of life in many patients (11,12). Drugs causing fatigue may exacerbate the problem.
- Clotting abnormalities – cholestatic patients can have a reduced ability to absorb fat-soluble vitamins including vitamin K (1,11,12). This may impair their clotting, making them more prone to bleeding (indicated by a raised prothrombin time and/or international normalised ratio (INR)) (1,13). Drugs such as anticoagulants and non-steroidal anti-inflammatory agents (NSAIDs) should be avoided in these patients, unless their clotting is normal. (1).

Cirrhosis

Patients with advanced cirrhosis can experience a wide range of complications including ascites, hepatic encephalopathy, variceal bleeding, clotting abnormalities, and hepatorenal syndrome (10,14,15). Each of these will bring with it a list of drugs that may need to be avoided or used with caution.

- Ascites – these patients are frequently started on low sodium diets and any intervention that increases sodium may be detrimental. Certain drugs, particularly effervescent tablets and some intravenous injections, have high sodium content (see Medicines Q&A 145.4) and are best avoided or used with caution in these patients. Drugs that inhibit salt and water excretion (e.g. NSAIDs) should also be avoided (1,14,15).
- Hepatic encephalopathy – is graded by severity based on changes in mental state, grade 1 patients showing signs of mild confusion, irritability and altered attention span through to grade 4 patients who are unconscious (10,16). Cirrhotic patients may have, or be at risk of, developing encephalopathy. Precipitating factors include electrolyte disturbances, constipation, and sedative agents (1,10,14,16,17). Consequently any drugs with the potential to cause these problems should be used with caution or avoided. Examples include diuretics and opioid analgesics (1,14,16,17) . Sedating drugs or those causing confusion may also

worsen the encephalopathy and/or mask the progression of encephalopathy through the grades (1,10).

- Varices - gastric and oesophageal varices develop in patients with portal hypertension and are prone to bleeding (10,14). Drugs that irritate the gastrointestinal tract, such as NSAIDs and bisphosphonates, expose the patient to an additional unwanted risk factor and should be avoided (1,9,10). Drugs that affect clotting should also be avoided (1,10).
- Clotting abnormalities - patients with decompensated cirrhosis have impaired clotting, primarily due to reduced synthesis of clotting factors by the liver. In addition, cirrhotic patients often suffer from thrombocytopenia (10). Drugs that affect clotting, cause thrombocytopenia or increase the risk of bleeding should be avoided or used with caution in these patients (e.g. anticoagulants, NSAIDs, antiplatelet agents) (1,9,10).
- Fatigue - is one of the most common symptoms of chronic liver disease, significantly affecting quality of life in many patients (11,12). Drugs causing fatigue may exacerbate the problem.
- Patients with cirrhosis and portal hypertension have an increased risk of developing renal impairment, therefore drugs that are potentially nephrotoxic (e.g. aminoglycoside antibiotics, NSAIDs) should be used with caution, if at all. Patients with hepatorenal syndrome should avoid nephrotoxic drugs altogether (1,3,9,10).

Acute Liver Failure

Patients in acute liver failure can suffer from encephalopathy, clotting abnormalities, ascites and hepatorenal syndrome and the guidance described within the “cirrhosis” section above can be used (10,18). It should be noted, however, that these patients are generally treated on intensive care units and treatment regimens may routinely include drugs that would in many situations ideally be avoided (e.g. ventilation and sedation, despite the precautions discussed under “hepatic encephalopathy” above) (19). Drug doses may need to be modified to ensure unnecessary accumulation does not occur e.g. load with normal doses of morphine but then titrate to the lowest effective dose.

Hepatitis

Conditions causing hepatocellular damage cover a range of disorders of differing severity, some acute and some chronic. Some patients may progress to acute liver failure or cirrhosis (1). The advice given above should then be applied.

- Clotting abnormalities - patients with severe hepatitis may have impaired clotting and a raised prothrombin time/INR. Drugs that affect clotting, cause thrombocytopenia or increase the risk of bleeding should then be avoided (e.g. anticoagulants, NSAIDs, antiplatelet agents) (1).

Alcohol Dependence

Patients who routinely consume large amounts of alcohol are at risk of acute alcohol withdrawal which can cause convulsions. In situations where acute alcohol withdrawal may occur (e.g. admission to hospital) it is wise to avoid drugs that lower the seizure threshold or increase the risk of seizures (1).

Summary

Patients with liver disease are susceptible to a number of complications (e.g. ascites, varices, encephalopathy). The risks of these occurring are dependent on the nature and severity of the liver disease. However, the side effects of drugs can exacerbate these complications, increasing the risk and worsening the patient’s condition. Once the type and extent of the patient’s liver dysfunction is fully understood, drug selection should involve consideration of some or all of the following classes of adverse effects: dermatological, endocrine/metabolic, gastrointestinal, haematological, neurological, and renal. The potential for drug-induced hepatotoxicity should be considered in patients with any form of liver disease, but some medicines known to be hepatotoxic may be used safely.

As well as taking the adverse effect profile into account, it is also important to consider any pharmacodynamic changes that the liver disease may cause, the effect it may have on a drug's pharmacokinetics, and patient-specific factors such as age, co-morbidities etc. The consequences of pharmacokinetic and pharmacodynamic changes on drug choice and dosing are discussed in Medicines Q&A What pharmacokinetic and pharmacodynamic factors need to be considered when prescribing drugs for patients with liver disease?

Limitations

The adverse effect profile of a drug cannot be considered in isolation. It is important to take into account pharmacokinetic and pharmacodynamic changes, and the patient's clinical condition. Understanding the nature and severity of a patient's liver condition using laboratory and biopsy results, results of scans (e.g. ultrasound), diagnosis (proven or suspected) and signs/symptoms of liver disease, is crucial before applying the principles of this Q&A.

References

(1) North-Lewis P, editor. Drugs and the Liver. London: Pharmaceutical Press; 2008, p85, 135-143, 148-150, 154, 157-169

(2) Zimmerman HJ. Hepatotoxicity-the adverse effects of drugs and other chemicals on the liver. Philadelphia: Lippincott Williams & Wilkins; 2nd edition 1999.

(3) Lee A. Adverse Drug Reactions. London: Pharmaceutical Press; 2nd edition 2006, p193-216

(4) Delco C, Tchambaz L, Schlienger R et al. Dose adjustment in patients with liver disease. Drug Safety 2005; 28(6): 529-545

(5) Bleibel W, Kim S, D'Silva K et al. Drug-induced liver injury: review article. Dig Dis Sci 2007; 52: 2463-2471

(6) Navarro VJ, Senior JR. Drug-related hepatotoxicity. N Engl J Med 2006; 354(7): 731-739

(7) Abboud G, Kaplowitz N. Drug-induced liver injury. Drug Safety 2007; 30(4): 277-294

(8) Fontana RJ. Acute liver failure due to drugs. Semin Liver Dis 2008; 28: 175-187

(9) Gupta NK, Lewis JH. Review article: the use of potentially hepatotoxic drugs in patients with liver disease. Aliment Pharmacol Ther 2008; 28: 1021-1041

(10) Walker R, Whittlesea C, editors. Clinical Pharmacy and Therapeutics. Churchill Livingstone; 4th edition 2007, p219-223, 225, 227

(11) Jones DJ. Complications of cholestasis. Medicine 2006; 35(2): 96-98

(12) Kaplan MM, Gershwin ME. Primary biliary cirrhosis. New Engl J Med 2005; 353(12): 1261-1273

(13) Kelly DA, Davenport M. Current management of biliary atresia. Arch Dis Child 2007; 92: 1132-1135

(14) Kumar P, Clark M, editors. Clinical Medicine. Elsevier Saunders; 6th edition 2005, p378-384

(15) Moore KP, Aithal GP. Guidelines on the management of ascites in cirrhosis. Gut 2006; 55:1-12

(16) Mullen KD, Ferenci P, Bass NM et al. An algorithm for the management of hepatic encephalopathy. Semin Liver Dis 2007; 27(suppl 2): 32-48

(17) Ferenci P. Treatment options for hepatic encephalopathy: a review. Semin Liver Dis 2007; 27(suppl 2): 10-17

(18) Stravitz RT. Critical management decisions in patients with acute liver failure. Chest 2008; 134: 1092-1102

(19) Bernal W, Auzinger G, Sizer E et al. Intensive care management of acute liver failure. Semin Liver Dis 2008; 28: 188-200

Quality Assurance

Prepared by

Emma Holmes (based on earlier work by Janet Tweed and Lucy Hennessy), Leeds Medicines Information Service, Leeds Teaching Hospitals Trust

Date Prepared

30th October 2020

Checked by
David Abbott, Leeds Medicines Information Service, Leeds Teaching Hospitals NHS Trust

Date of check
30th October 2020

Search strategy
Original search

- Embase:
  1. [exp *LIVER DISEASE or exp *BILIARY TRACT DISEASE] and [exp DRUG THERAPY] [Limit to: Publication Year 2000-2009 and Priority Journals and English Language and (Publication Types Review)]
  2. [[exp *ADVERSE DRUG REACTION or exp *DRUG TOXICITY or exp*SIDE EFFECT] and [exp *LIVER DISEASE or exp *BILIARY TRACT DISEASE]] not [search 1. prior to limits] [Limit to: Publication Year 2005-2009 and English Language]
- Medline:
  1. [exp *LIVER DISEASES or exp *BILIARY TRACT DISEASES] and [exp *DRUG THERAPY/ae or exp *DRUG TOXICITY] [Limit to: English Language and Human]
  2. [[exp *LIVER DISEASES or exp *BILIARY TRACT DISEASES] and [exp *DRUG THERAPY]] not [exp *DRUG INDUCED LIVER DISEASE/ci or exp *BILIARY TRACT DISEASES/ci] [Limit to: English Language and Humans and Publication Year 2005-2009 and Core Clinical Journals]
  3. [[exp *LIVER DISEASES or exp *BILIARY TRACT DISEASES] and [exp *DRUG THERAPY]] not [exp *LIVER DISEASES/ci or exp *BILIARY TRACT DISEASES/ci] [Limit to: English Language and Humans and Publication Year 2005-2009 and Review Articles]
  4. [exp *LIVER DISEASES or exp *BILIARY TRACT DISEASES] [Limit to: English Language and Humans and Publication Year 2005-2009 and Review Articles and Core Clinical Journals]
- Pharmline: "Liver Diseases" and “Adverse Effects” [Limit by year: 2000-2009]
- NELM: Liver. www.nelm.nhs.uk, accessed 14/09/2011
- NLH: Liver diseases;cirrhosis;ascites;varices;encephalopathy;cholestasis;primary sclerosing cholangitis;hepatitis. http://www.library.nhs.uk/, accessed 18.3.09
- Clinical expert: Penny North-Lewis, Lead Paediatric Liver Pharmacist, Leeds Teaching Hospitals NHS Trust, Leeds.

Updated search

- Embase:
  3. [*LIVER DISEASE or *BILIARY TRACT DISEASE] and [*DRUG THERAPY] [Limit to: Priority Journals and English Language and (Publication Types Review)]
  4. [*ADVERSE DRUG REACTION or *DRUG TOXICITY or *SIDE EFFECT] and [*LIVER DISEASE or *BILIARY TRACT DISEASE] [Limit to: English Language]