Collectively, liver function tests can help clarify a clinical picture

In our continuing series, which aims to help remind you of basic pharmacy skills, Angela Burgin explains the commonly used liver function tests and how they should be interpreted.

Introduction

The liver has many physiological functions including the synthesis of clotting factors, fat metabolism, cholesterol synthesis, and glucose control. In addition to this, it plays a large role in physiological drug use. Liver function tests (LFTs) are a set of biochemical tests that together can indicate whether inflammation or damage has occurred within the liver and its associated systems, such as the biliary tract. They can also give some indication of the functionality of the liver and can be used as an aid to drug dosing, prediction of physiological drug handling (metabolism and excretion) and ultimately are essential when monitoring for adverse effects of certain drugs.

Individual blood tests

A request for LFTs will usually include the following tests; albumin, bilirubin, alkaline phosphatase, transaminase enzymes (alanine aminotransferase and aspartate aminotransferase), gamma-glutamyl transferase and some clotting factors (see Table 1 — ranges given are those used at the Salford Royal Hospital Trust biochemistry laboratories). The reference ranges given in Table 1 are typical ranges but they vary between different laboratories. When interpreting test results, you should always use the reference ranges given locally.

It is worth noting at this point that there are multiple physiological sources of each enzyme (as detailed in Table 1).[1,2] For this reason a change in individual liver enzyme levels can be difficult to interpret if read alone. However, when read in combination a much clearer picture can be deduced.

Albumin

Albumin accounts for more than half of plasma proteins.[1,2] It is produced only by the liver and has a long half-life of around 20 days.[2,3] An acute liver insult will produce no change in albumin levels. In chronic liver disease and severe malnutrition, however, albumin production is reduced.

There are many other factors that can reduce albumin levels. These include increased breakdown secondary to trauma or malignancy, increased excretion, for example through the kidneys (proteinurea) or in severe burns and altered distribution secondary to excess fluids.[1,2]

Because albumin acts as a carrier for many drugs (such as warfarin and phenytoin) reduced albumin levels can increase circulating free drug resulting in increased drug toxicity.

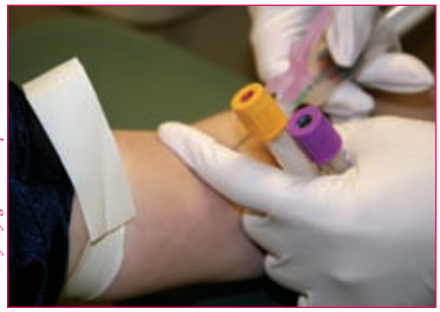
Bilirubin

Bilirubin is a by-product of red blood cell breakdown. It is very lipid soluble and is heavily excreted through the biliary system. It is carried within the plasma by albumin to the liver where it is conjugated by glucuronidation to form water soluble bilirubin. After transportation to the small intestine conjugated bilirubin is hydrolysed to free bilirubin, which is further reduced to urobilinogen. This is then either excreted in the faeces, reabsorbed into the enterohepatic circulation or renally excreted.[3]

Table 1. A summary of liver function tests[1,2]

Test	Typical ranges	Physiological location	Indication in relation to liver disease
Albumin	35–50 g/l	Plasma	Produced by liver — good indicator of functionality of the liver
Total Bilirubin	0–20 micromol/l	Plasma	Elevation can be caused by many factors
Alkaline Phosphatase (ALP)	30–130u/l	Liver, biliary tract, bones, gastro-intestinal tract	Enzyme released from liver and biliary tract
Alanine aminotransferase (ALT)	2–50u/l	Liver, cardiac muscle, skeletal muscle	Enzyme released during hepatocellular damage
Aspartate aminotransferase (AST)	0–35u/l	Liver, skeletal muscle, kidneys, cardiac muscle, red blood cells	Enzyme released during hepatocellular damage
Gamma-glutamyl transferase (GGT)	<60u/l	Liver, kidneys, prostate gland, pancreas	Relatively non-specific

Subsequently, low circulating albumin levels and/or damage to the liver can hinder bilirubin excretion and will result in elevated bilirubin levels. Bilirubin levels of more than 35 micromol/l can result in visual signs of jaundice.[1,2] This may be the first sign to a patient that something is wrong with their liver. Monitoring bilirubin in such patients is useful because normalisation of bilirubin is a good indicator that the problem is resolving, even though the patient may still look jaundiced.



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Increased bilirubin levels can be caused by increased haemolysis, reduced ability of the liver to conjugate bilirubin (such as occurs in cancer or hepatitis) or by blockage of the biliary tract (eg, cholestasis).[2]

Alkaline phosphatase

Because this enzyme is released from bone as well as liver it is elevated in Paget's disease and in patients with bone metastases.[1,2]

Transaminase enzymes: AST and ALT

These enzymes are not always included in the LFT request because of their lack of specificity. This is more the case for AST than ALT.

Gamma-glutamyl transferase

This test is relatively non-specific and is used infrequently. If gamma-glutamyl transferase (GGT) is raised in combination with an increase of all other liver enzymes then GGT adds no further insight to an interpretation of liver function tests. It can be used in combination with alkaline phosphatase (ALP) to aid disease diagnosis of hepatic or non-hepatic origin. An increase in both ALP and GGT is indicative of cholestasis. An increase of ALP with normal GGT would indicate bone pathology.[3]

GGT release is stimulated by some drugs (such as phenytoin and carbamazepine) and by the consumption of alcohol. As a result of the latter, it has some use in assessing abstinence in alcoholics.

Clotting factors

Clotting factors are a good indicator of liver functionality because they are produced by the liver.[3] Prolonged clotting times are a sign of a chronic liver problem and pose an increased bleeding risk. It is essential to consider these factors when assessing patient requirements for anticoagulants or anti-platelets, and when patients are prescribed medicines that could increase bleeding risk further, such as non-steroidal antiinflammatories (NSAIDS).

Take a systematic approach to interpreting LFTs

The important point to remember when interpreting LFTs is that no test should be taken and read in isolation. It is imperative when trying to determine a diagnosis that each test should first be looked at individually and then a pattern established collectively. Table 2 gives some guidance regarding the enzyme levels in different clinical situations. This table is not exhaustive and is intended as a guide only.

Pre-existing liver disease

Discussion of treating liver disease is beyond the scope of this paper. What we should consider here, however, are the possible actions to take when we come across patients with pre-existing liver disease. For each medicine prescribed the route of metabolism and excretion should be considered along with protein binding, clotting and hepatotoxicity potential. When reviewing prescriptions for patients with pre-existing liver disease the *BNF* (Appendix 2)[4] and individual drug data sheets (SPCs) are useful starting references.

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Problems begin to arise when patients have complications of liver disease such as ascites, obstructive jaundice or signs of encephalopathy. These symptoms often can be exacerbated, or side-effects of medication can be enhanced when certain drugs are administered concomitantly. For example, administration of opioid analgesics or sedatives may further impair cerebral function in a patient with hepatic encephalopathy. Also, NSAIDs or corticosteroids could further exacerbate ascites.

When things go wrong with medicines and the liver

The liver is heavily involved in the metabolism and excretion of many medicines. Substances that are absorbed from the gastrointestinal tract will be transported to the liver (through the hepatic vein) where they will undergo first-pass metabolism before entering the systemic circulation. As

Table 2. LFT derangement in different physiological situations[1–3]

ALT	ALP	GGT	Albumin	Bilirubin	Possible indication
↑↑↑	↑	↑	Normal	Normal or ↑	Acute liver disease
Normal or mildly raised	↑	↑	↓↓	↑↑↑	Chronic liver disease/ alcoholic liver disease
Normal	↑↑↑	↑↑↑	Normal	↑↑↑	Obstructive jaundice/ Cholestasis
		↑↑↑			Enzyme inducing drugs (such as phenytoin) or recent alcohol intake

Key: ↑ = *Mildly raised* ↑↑ = *Moderately raised* ↑↑↑ = *Severely raised*

Table 3. Suggested liver function monitoring for some common drugs[6]

Drug	Monitoring requirement
Statins	Baseline, within 1–3 months then at 6-monthly intervals for 1 year. Re-check 12 weeks after any dose increase
Carbamazepine	Baseline LFTs then periodically
Phenytoin	Baseline LFTs then periodically
Sodium valproate	Baseline then every six months
Amiodarone	Baseline then every six months
Warfarin	Baseline and whenever there is a change in clinical picture, eg, liver problems
Olanzapine	Baseline then every 12 months
Risperidone	Baseline then every 12 months
Methotrexate	Baseline then monthly thereafter
Azathioprine	Baseline then weekly for six weeks, then fortnightly until stable for six weeks. Once stable, monthly. If dose is altered, then check two weeks after dose change then every month
Leflunomide	Baseline, monthly for first six months then every 12 months when stable. If taking another immunosuppressant or hepatotoxic drug, then check LFTs every month

a result the liver may incur injury secondary to medication or ingested products (for example, alcohol).

It is difficult to estimate the metabolic ability of the liver from the results of LFTs. Each case should be taken on an individual basis. For example, patients who are taking simvastatin may have a mild asymptomatic increase in serum transaminases (for example, ALT) which would not require any action.[5] Discontinuation of the medicines would be indicated if the enzymes were three times the upper limit of normal.[5]

Some medicines can result in acute liver damage or cholestasis. The most common drugs that may cause this are rifampicin, isoniazid and NSAIDs. Other medicines that can cause liver damage are paracetamol (usually in situations of overdose), amiodarone, sodium valproate, phenytoin, statins and carbamazepine. With these medicines monitoring of liver function is essential. Cholestatic hepatitis can also occur with antibiotics such as co-amoxiclav and flucloxacillin.

Table 4. Some enzyme inducing or inhibiting drugs

Enzyme inducers	Enzyme inhibitors
Alcohol	Amiodarone
Carbamazepine	Cimetidine
Chlorpromazine	Sodium Valproate
Phenytoin	Sulphonamides
Rifampicin	

Monitoring of LFTs and medicines

The monitoring of LFTs for some medicines are listed in Table 3 — these data were produced by a collaboration between London and South East Medicines Information service, South West Medicines Information Service and Croydon Primary Care Trust and is available on-line.[6] Referring to individual drug datasheets is necessary to determine when and what action is needed if LFTs become deranged.

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Some medication can affect hepatic drug metabolism. These medicines can result in hepatic enzyme induction or enzyme inhibition. Induction of enzymes within the liver may result in reduced levels of certain drugs. For example, rifampicin, an enzyme inducer, will reduce circulating levels of warfarin or the combined oral contraceptive pill[4] because it increases their metabolism. Some antiepileptic drugs, such as carbamazepine and phenytoin, can result in increased self-metabolism. As a result drug plasma levels may need monitoring and doses may need to be increased.

Medicines that inhibit drug metabolism may result in increased circulating levels of other medicines and thus increase their side-effect profile. For example, amiodarone will reduce the metabolism of phenytoin resulting in raised circulating phenytoin levels.[4] Combined with the non-linear kinetics of phenytoin this may result in phenytoin toxicity. Some medicines that can induce or inhibit liver enzymes are listed in Table 4.

Conclusion

The liver is an important organ with regard to medication metabolism and excretion. LFTs are a very useful tool when assessing liver damage and functionality. They should be read in isolation first and then interpreted collectively to establish a full clinical picture. They can assist in diagnosis, in regulating dosing of medication and are useful when assessing patient symptoms that are thought to be side-effects of a medication.

Declarations of interest

The author has no interests to declare.

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