Drug therapies in liver disease

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ABSTRACT – The likelihood of a general physician encountering a patient with compensated and decompensated liver disease is increasing. This article provides an overview of pharmaceutical agents currently used in the management of cirrhosis and is designed to allow a better understanding of the rationale for using certain drugs in patients with often complex pathology.

KEY WORDS: Cirrhosis, pharmacology, hepatic encephalopathy, variceal haemorrhage, ascites

Introduction

The increase in mortality resulting from liver disease in the UK is a worrying phenomenon that is at odds with other conditions, such as cardiovascular disease and cancer, which have seen increases in survival due to improved medical care. The continued upward trend means that the recognition and management of the complications of chronic liver disease will become more commonplace for all physicians. In this article, I outline the pharmaceutical agents used to manage the common manifestations of advanced liver disease. We have not described newer drugs used to treat specific aetiologies (the recent advances in the treatment of hepatitis C alone are worthy of an extended review) because these are likely to remain the remit of the specialist hepatologist.

Treatment of ascites

Ascites affect 50% of patients with cirrhosis after 10 years of follow up.1 Diuretic therapy in combination with dietary salt restriction (2 g/day) is the mainstay of treatment and only patients who are truly resistant or intolerant of pharmacological therapy should be considered for large-volume paracentesis and other therapies. In situations where there is a large reversible component, the diuretic requirement might diminish with management of the underlying liver disease.

The pathophysiological process is complex. Increased nitric oxide and other vasodilator molecules cause progressive peripheral and splanchnic arterial vasodilatation, leading to an effective reduction in the circulating blood volume.2 Compensatory vasoconstricting mechanisms include the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system,3 which stimulate renal sodium and water retention, leading to expansion of the extracellular fluid compartment. Portal hypertension also drives fluid redistribution into the peritoneal space. If left untreated, these changes can increase the risk of hepatorenal syndrome.

Diuretics

Spironolactone

Cirrhosis is an acquired state of secondary hyperaldosteronism. Spironolactone (an aldosterone antagonist) blocks sodium reabsorption along the distal renal tubule, thus targeting one of the key maladaptive pathways (the RAAS) of ascites accumulation. Spironolactone produces a more profound natriuresis and diuresis compared with loop diuretics, such as furosemide. In a randomised study, spironolactone was shown to be more efficacious compared with furosemide, in that 95% vs 52% of patients showed a clinical response.4 British and European guidelines recommend a starting dose of 100 mg/day titrating up to a maximum of 400 mg/day.5,6 Adverse effects include hyponatraemia, hyperkalaemia, gynaecomastia and gastrointestinal disturbance. Anti-androgenic adverse effects include lethargy, decreased libido and menstrual irregularity.

Amiloride

Amiloride is a potassium-sparing diuretic that tends to be used as a second-line agent when spironolactone cannot be used because of gynaecomastia. It has a different mode of action to that of spironolactone, exerting its effect on the proximal renal tubule and it can be more effective in patients with low levels of plasma aldosterone.7 The dose range is 15–30 mg daily. Adverse effects include hyperkalaemia, gastrointestinal disturbance and postural hypotension.

Furosemide

In advanced liver disease, renal perfusion becomes progressively more compromised and sodium reabsorption from the proximal renal tubule becomes a more important factor, at which point combination therapy with spironolactone and a loop diuretic might be required.8 Anecdotally, furosemide is more effective when there is disproportionately more peripheral oedema. Furosemide is typically started at 40 mg/day and titrated to a maximum of 160 mg/day. Adverse effects include hypotension, acute kidney injury and postural hypotension.

Whether to initiate spironolactone and a loop diuretic together or to adopt a stepwise sequential approach (ie titrate to the maximum dose of spironolactone then add in furosemide)
divides international opinion. A randomised study recommended sequential treatment because it required fewer dose adjustments, with no difference in the frequency of adverse events. Most patients in this study had a first presentation of ascites. A more recent randomised study in patients with cirrhosis, but without renal failure, reached the opposite conclusion, finding that combination therapy produced a more rapid mobilisation of ascites, with a lower incidence of hyperkalaemia. In this study, most patients had recurrent ascites.

These data suggest that patients with a first presentation of ascites and well-preserved renal function will respond adequately to spironolactone alone, and this approach is most suited to an outpatient setting. Patients with long-standing ascites or a reduced glomerular filtration rate (GFR) will have quicker symptom relief with combination therapy.

All patients taking diuretic therapy remain at risk of renal dysfunction and hyponatraemia, and should have appropriate monitoring. Although low plasma sodium is well tolerated in cirrhosis, diuretics should be continued unless serum sodium levels fall to <120 mmol/l or serum creatinine levels increase significantly.

Emerging therapies

Vasopressin 2 receptor antagonists

‘Vaptans’ are relatively novel drugs first used in patients with hyponatraemia with oedema. Observations were made that, in some patients with cirrhosis, ascites also improved. Blockade of vasopressin 2 receptors causes favourable haemodynamic effects; for example, vasoconstriction of splanchnic and systemic vessels increases renal perfusion and improves ascites. Tolvaptan used for 7 days in combination with standard diuretic therapy has been shown in a recent phase III trial to improve ascites and serum sodium. Reported adverse effects in the tolvaptan group were thirst, constipation, renal impairment, diarrhoea, urinary frequency, pyrexia, hepatic encephalopathy, vomiting, insomnia, stomatitis and pruritus.

A recently published meta-analysis of 12 industry-funded trials with over 2,000 participants showed that use of vaptans (tolvaptan, satavaptan and lixivaptan) in patients with cirrhosis was associated with modest clinical benefit and increases in only serum sodium.19 Reported adverse effects in the tolvaptan group were thirst, constipation, renal impairment, diarrhoea, urinary frequency, pyrexia, hepatic encephalopathy, vomiting, insomnia, stomatitis and pruritus.

Midodrine is an α1 adrenoceptor agonist that increases peripheral vascular resistance and has also been shown to increase renal perfusion and renal sodium excretion. There are randomised trial data suggesting that both midodrine and clonidine were superior to standard medical therapy in terms of controlling ascites.14

Treatment of spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis (SBP) is a frequent complication of cirrhosis and portal hypertension, indicating an advanced stage of liver disease and poorer prognosis. Clinical presentation ranges from asymptomatic to local abdominal tenderness to septic shock.

Bacterial translocation from the gastrointestinal tract to mesenteric lymph nodes and then to ascitic fluid is the most common cause of SBP. There are several factors that promote SBP in patients with cirrhosis and portal hypertension, including alterations in faecal microbiota, increased intestinal permeability and deficiencies of the cellular and humoral immune system.

Antimicrobials

Given that a pathogen is isolated in only 40% of patients with SBP,9 empirical antibiotics should be started immediately. Cefotaxime, a third-generation cephalosporin, has been most widely studied and has excellent coverage of the typical organisms. A dose of 2 g intravenously twice daily is as effective as 1 g four times daily. Amoxicillin/clavulanic acid appears to be equally efficacious compared with cefotaxime when examined in a single trial involving 80 patients. No adverse effects were observed in either group.

Ciprofloxacin has similar success rates to the antimicrobials mentioned above and has good oral bioavailability. Adverse effects of quinolones include tendonitis, tendon rupture and a prolonged QTc interval. A head-to-head comparison of oral ofloxacin and intravenous cefotaxime showed that there was no difference in outcome. However, this study was restricted to patients with uncomplicated SBP and intravenous therapy might be more appropriate in severe cases. Most hepatologists avoid the use of aminoglycosides because of the risk of nephrotoxicity in patients at severe risk of hepatorenal syndrome (HRS) and other acute renal injury.

Given that recurrence of SBP is common (up to 70% within 12 months), prophylaxis is advised to maintain intestinal decontamination. Antibiotic prophylaxis risks promoting the development of resistant organisms and Clostridium difficile, but has been demonstrated to improve survival in those patients with previous SBP and those with low protein ascites (<10 g/l) who are at high risk of developing SBP.20

Both ciprofloxacin (750 mg/week) and norfloxacin (400 mg/day) are effective as prophylaxis. Meta-analysis of trials using quinolones suggests that the number needed to treat is 8.4 to prevent one episode of SBP and 8.6 to prevent one death at 6 months.21

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Although most of these studies pre-date the emergence of hospital-acquired infection as a significant public health issue, significant C. difficile infection has seldom been reported in clinical trials. If resistant organisms are cultured or a patient is not responding clinically, consultation with a microbiologist and switching antibiotics should be considered.

Other agents

Rifaximin
Alterations in faecal microbial composition represent a potential modifiable factor. So far, studies evaluating the use of the non-absorbable antibiotic rifaximin seem promising. Used as primary prophylaxis in an open-label study of 404 patients, rifaximin reduced the risk of SBP from 89% to 68% at 1 year compared with placebo. It is a well-tolerated drug and, in this patient group, is an attractive, if costly option to provide dual prophylaxis against hepatic encephalopathy (HE) and SBP.

Probiotics
Probiotics have been studied as an adjunct in combination with norfloxacin, but they did not offer additional benefit in terms of reducing the incidence of SBP. Repopulating the colon with less pathogenic organisms remains an attractive non-pharmacological approach to both SBP and HE treatment.

Cisapride
In a rodent model, cisapride, a serotonin 5-hydroxytryptamine receptor 4 receptor agonist, reduced bacterial translocation via effects on intestinal permeability and motility. However, it is unlikely to be studied in humans because of its cardiac adverse effects. Therefore, other prokinetics have a theoretical benefit, but have not been formally studied.

Treatment of hepatorenal syndrome

HRS is a liver-specific condition but only one of the multiple causes of acute kidney injury in patients with acute or chronic liver disease. The syndrome is triggered by portal hypertension, which in turn causes arterial vasodilatation. One proposed mechanism is an increased action of vasodilators resulting in decreased vascular resistance in the splanchnic circulation and a reduction in the total vascular resistance. Despite the compensatory renal vasoconstriction, there is an overall reduction in renal perfusion, which results in a fall in the GFR.

There are two recognised types of HRS. Type 1 HRS is usually diagnosed when serum creatinine increases more than 100% from baseline to a final level >133 μmol/l within a period of 2 weeks. By contrast, type 2 HRS occurs in patients with refractory ascites and a slower deterioration in renal function, with a serum creatinine value of >133 μmol/l.

Prompt identification of HRS and exclusion of other causes of renal failure are paramount because the prognosis is poor. Diuretics should be stopped and, ideally, central venous pressure should be monitored to guide fluid and albumin administration. All patients should be screened for sepsis.

Vasoactive drugs

Terlipressin
For patients not admitted to intensive care units, the pharmacological therapy of choice is terlipressin. This vasopressin analogue reduces splanchnic vasodilatation with the therapeutic aim of increasing the mean arterial pressure by 10–15 mmHg. A recent meta-analysis showed that terlipressin significantly improves reversal and survival of patients compared with no therapy or albumin alone.

Recommended dosing is 0.5–1 mg every 4–6 h, titrating to urine volume and serum creatinine. Treatment should not extend beyond 14 days and should be discontinued when serum creatinine is <133 μmol/l. Maximum benefit is seen when treatment is combined with albumin administration at 1 g/kg for 24–48 h (up to a maximum of 100 g/day), followed by 20–40 g/day.

Terlipressin is contraindicated in those with severe arteriopathy and should be used with caution in those patients with cardiac arrhythmias and coronary artery disease.

Noradrenaline
Although the efficacy and safety of noradrenaline is similar to that of terlipressin, it is usually reserved for the intensive care setting. Noradrenaline is used as a continuous infusion of 0.5–3 mg/h and should be used with albumin as above. The aim is to increase the mean arterial pressure by 10 mmHg.

Midodrine
Midodrine, also mentioned above, has the advantage of being an oral agent that is suitable for the non-acute setting. Although midodrine has been shown to be effective in the management of HRS, this was in combination with albumin and octreotide, and its efficacy in prevention of recurrent HRS has yet to be explored.

Renal replacement therapy and transplantation

Renal replacement therapy is not associated with improved survival in patients with HRS, but has been used, if indicated, as a bridge to liver transplantation. It is often advocated that it is important to rule out other forms of acute liver injury that might respond well to renal replacement and, although mortality remains high, there are intriguing suggestions that HRS per se is not associated with a worse outcome in patients on dialysis, although published data remain scarce.

Treatment and prevention of variceal bleeding

Portal hypertensive bleeding from oesophageal or gastric varices is an important cause of mortality in patients with advanced liver disease. Liver fibrosis increases intrahepatic vascular resistance, which in turn elevates portal pressure and increases the difference between hepatic venous inflow and outflow pressure (referred to as the hepatic venous pressure gradient [HVPG]). Advanced liver disease, variceal diameter and tension in the wall of the vessel increase the risk of
bleeding, but other factors, such as bacterial endotoxin release, might also have a role in triggering a bleeding episode. Although endoscopic therapy and salvage portosystemic shunting are definitive treatments, two pharmacological therapies have been shown to have an impact on survival. Pharmacological treatment has the advantage of not requiring specialist teams and can be given rapidly while the patient is being resuscitated and emergency endoscopy is arranged.

Treatment of variceal bleeding

Vasoactive drugs

The vascular physiology of the cirrhotic liver is complex, but can be best described as an imbalance between intrahepatic vasoconstriction and systemic and splanchnic vasodilatation. Vasoactive drugs lead to an acute reduction in portal pressure by reducing splanchnic blood flow, thus lowering portal pressure and the HVPG. Both vasopressin and somatostatin are both hormones that can lower HVPG but the use of vasopressin is associated with unacceptable cardiovascular vasoconstriction and somatostatin has only a transient effect requiring continuous infusion. Both hormones have been superseded by synthetic analogues.

Octreotide and vrapreotide, both long-acting analogues of somatostatin, have been used in the treatment of variceal bleeding, particularly in those countries where vasopressin analogues were unlicensed. Octreotide has been demonstrated to be as efficacious as terlipressin in improving the control of variceal bleeding, but not when compared with endoscopy alone.34 Early administration of vrapreotide has been shown in one French study to reduce the need for blood transfusion and to improve control of variceal bleeding.35

Meta-analysis has demonstrated that terlipressin (a long-acting analogue of vasopressin) leads to a 34% relative risk reduction in mortality compared with placebo. However, it has not been demonstrated that terlipressin is superior to octreotide, somatostatin or endoscopic treatment alone.36 Terlipressin is more widely available in the UK and the recommended dosing regimen is simpler than that of octreotide or somatostatin: bolus vs continuous infusion. The recommended dose is 1–2 mg four times daily. The optimal duration for continuing treatment post endoscopy is not known and guidelines recommend between 3 and 5 days.37,38 Significant adverse effects include cardiac and peripheral ischaemia.

Meta-analysis also demonstrated that vasoactive drugs in combination with endoscopic therapy is superior to endoscopic therapy alone in terms of initial control of bleeding and 5-day rebleeding rates, but does not change overall mortality.39

Antibiotics

Bacterial infection can have a role in triggering variceal haemorrhage. A Cochrane review of 12 trials demonstrated that antibiotic prophylaxis decreases all-cause mortality, mortality from infections, rebleeding rates and length of stay.40 Oral quinolones or intravenous cephalosporins have been the traditional antimicrobial of choice. There is some evidence to suggest that ceftriaxone is superior to norfloxacin in that fewer patients given ceftriaxone subsequently developed proven infection, although no difference in mortality has been shown.41 Another advantage of cephalosporins might be a decreased incidence of C. difficile. In most studies, antibiotics were given for 5–7 days.

Prophylaxis of variceal bleeding

Rebleeding is highly likely to occur if there is no further treatment following an index bleed. Data from control groups indicate that approximately two-thirds of patients will rebleed at 2 years, leading to significant mortality (33%).42

Non-selective β-adrenoceptor blockers

Non-selective β-adrenoceptor blockers (NSBBs) are the mainstay of prophylaxis. NSBBs reduce portal pressure by decreasing cardiac output and producing splanchnic bed vasodilatation. A decrease in portal pressure is accompanied by a drop in intravariceal pressure and, hence, the risk of bleeding is reduced.43 They are effective and safe used alone, or in combination.

Selective β-adrenoceptor blockers are suboptimal and not recommended. Recent trials of carvedilol, an NSBB with mild anti-α 1-adrenergic effects, have shown a possible advantage over propranolol in terms of a reduction in the HVPG, although it can cause higher rates of systemic hypotension.44 Propranolol 40 mg twice daily, nadolol 20 mg/day or carvedilol 12.5 mg/day are typical starting doses.

NSBBs are low in cost and do not require specialist expertise for use. However, 15–20% of patients develop adverse effects. HVPG studies have shown that almost half of patients with cirrhosis are ‘haemodynamic non-responders’, in that they fail to achieve a therapeutic reduction in HVPG <12 mmHg.45

Nitrates

Although they are potent vasodilators, meta-analysis has not demonstrated that nitrates lead to a reduction in index bleed or rebleeding rates, but show a possible survival benefit for secondary prophylaxis.46 Their role tends to be restricted to haemodynamic non-responders. It is difficult to identify these patients and, hence, nitrates are rarely used. Adverse effects include postural hypotension, headaches and sleep disturbance.

Simvastatin

The relative frequency of adverse effects with NSBBs and mixed results with nitrates have stimulated a search for other agents to lower portal pressure. Simvastatin has been shown in a small randomised trial to be superior to placebo in lowering HVPG over 1 month.47 The purported mechanism is a reduction in intrahepatic vascular resistance. Statins are an attractive agent, because they are well tolerated and are frequently prescribed to modify cardiac risk profiles, which can coexist in liver disease (eg secondary to non-alcoholic steatohepatitis).
**Angiotensin antagonists**

Activation of the RAAS contributes to intrahepatic vascular resistance. As such, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) can target this pathophysiological mechanism. Meta-analysis has shown these drugs to cause a similar reduction in HVPG when compared with NSBBs in Child Pugh A cirrhosis. This effect was not seen in Child Pugh B and C, where acute kidney injury was frequently reported.48 Evidently, careful patient selection will be key if larger studies demonstrate clinical benefit.

**The treatment of hepatic encephalopathy**

Hepatic encephalopathy (HE) is the neuropsychiatric manifestation of both acute and chronic liver disease and is a cause of considerable mortality and disabling morbidity. The clinical manifestations range from mild cognitive impairment and sleep–wake cycle disturbance to coma and fatal cerebral oedema.49

Precipitants of HE include constipation, infection, gastrointestinal bleeding, sedative use and electrolyte disturbance, and these factors should be actively looked for and treated aggressively. Low protein diets were once advocated in the treatment and prevention of HE, but it is now recognised that high calorie and protein diets are well tolerated in patients with cirrhosis49 and should be encouraged to counteract the pathological cachexia associated with advanced disease.

The pathophysiology of HE is complex, but it is generally held that increased ammonia levels contribute to cerebral inflammation and neurotoxic injury.51 Ammonia levels are thought to be influenced by a lack of functional hepatocytes to perform ammonia detoxification and increased delivery to the cerebral circulation because of portosystemic shunting. Therapeutic strategies have traditionally focused on reducing ammonia production or its absorption from the gastrointestinal tract, whereas newer treatments aim to improve ammonia metabolism to reduce its toxic effects.

**Strategies designed to reduce portal ammonia absorption**

**Laxatives**

Non-absorbable disaccharides are the most widely advocated substance for the treatment of HE and its use features in most international guidelines.52 Despite this, the evidence for their efficacy is limited. The removal of ammonia and other nitrogenous compounds with bowel cleansing has long been advocated. The drug of choice is lactulose, which has further theoretical advantages, including acidification of the colon promoting non-ammoniagenic colonic flora and sequestration, and subsequent elimination of ammonia salts. Lactulose should be given orally or nasogastrically in sufficient amounts (30–40 ml three to four times daily) to promote at least three bowel evacuations per day. Lactulose enemas are of little extra benefit, are difficult to administer and have largely been superseded by the use of phosphate enemas in higher-grade HE. Despite their universal adoption, the evidence behind the use of non-absorbable disaccharides is limited and a large meta-analysis found that it was of no benefit.53 Subsequent authors have attempted to refute this54 and a lack of appetite for further studies, as well as the low cost of this treatment approach, means that it is unlikely to disappear from clinical practice. Long-term compliance with lactulose therapy is often hampered by diarrhoea and gaseous distension, and dehydration and electrolyte disturbance can precipitate further attacks of HE.

**Antibiotics**

The removal of ammoniagenic bacteria from the gut can be achieved by the use of non-absorbable antibiotics. Neomycin was the first drug widely used in the treatment of HE, but its toxicity with long-term use has led to it being superseded by rifaximin. Rifaximin has a broad spectrum of action in vitro and has been shown to be effective at reducing overt HE and hospitalisations resulting from HE.55 In January 2013, a rifaximin-alpha preparation was licensed for the treatment of HE at a dose of 550 mg twice daily and is currently undergoing appraisal by the National Institute for Health and Care Excellence.

**Probiotics**

There has been recent interest in the use of probiotics and related products to treat several gastrointestinal disorders, including HE. Non-urease-containing bacteria with or without co-administration of fermentable fibre (synbiotics) have several theoretical modes of action, including displacing nitrogen-producing bacteria, favourably affecting luminal pH and restoring the gut–portal venous barrier. Although some small-scale studies have demonstrated a modest effect on blood ammonia levels and episodes of HE, there is yet to be a strong body of evidence to support the routine use of these products.56

**Strategies to modulate ammonia metabolism**

Where liver function is impaired, there is a net gain in circulating ammonia caused by increased absorption from the gut and failure of normal hepatic nitrogen metabolism. Other organs (most notably skeletal muscle) are able to convert ammonia into less toxic metabolites and the promotion of these metabolic pathways has been shown to be an effective therapy for HE, initially in patients with inborn errors of the urea cycle, but latterly in patients with HE resulting from global liver impairment.

**Phenylbutyrate**

Phenylbutyrate is converted to phenylacetate in vivo and can reduce HE in situations where glutamine levels are high by facilitating glutamine excretion (thus removing it as a source of ammonia production). Although effective in some inborn errors of metabolism, its use in chronic liver disease is not proven.

**Sodium benzoate**

Sodium benzoate increases the renal excretion of ammonia and, in one small study, demonstrated equal efficacy to lactulose in the treatment of HE.57
L-ornithine L-aspartate

The administration of L-ornithine L-aspartate (LOLA) treatment provides substrate for the conversion of ammonia into urea and glutamate, which are less toxic and more readily excreted. This approach has shown promise in patients with severe or refractory HE. Some studies have demonstrated that a postprandial infusion of 20–40 g LOLA results in reduced blood ammonia levels and improvement in HE grade,\(^{58}\) but there remain concerns about the induction of hypoglycaemia and rebound hyperammoniaemia on cessation of treatment. Until these concerns are fully addressed, LOLA should not be considered a routine treatment for HE.

Other drugs

Acarbose

In patients with coexisting diabetes mellitus, acarbose (which inhibits gut glucose absorption and promotes non-ammoniagenic intestinal flora) has been shown to lower blood ammonia levels and improve HE.\(^{69}\) However, it is unlikely to be more effective than the standard therapies used to alter gut flora outlined above.

Flumazenil

This benzodiazepine antagonist has shown some efficacy in patients with severe HE and is thought to exert its effect through the restoration of central dopaminergic function.\(^{60}\) Clearly, it is likely to be of most benefit in patients in whom benzodiazepine use is suspected of precipitating HE.

Conclusion

Patients with liver disease should be cared for by a multidisciplinary team led by a clinician with experience of caring for patients who have complex healthcare needs. The generalist is likely to encounter these patients more frequently because of the increasing incidence of liver disease. As understanding of the complex pathology underpinning fibrogenesis and portal hypertension improves, novel therapies are awaited that could halt or reverse these processes to add to the existing drugs in the current armamentarium against liver disease.

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