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REVIEW

Safe use of medication in patients with cirrhosis: pharmacokinetic and pharmacodynamic considerations

Rianne A. Weersink [a,b], David M. Burger[c], Kelly L. Hayward[d,e], Katja Taxis[a], Joost P.H. Drenth[f] and Sander D. Borgsteede[b]

[a]Department of Pharmacy, Unit of Pharmacotherapy, -Epidemiology and -Economics, University of Groningen, Groningen, The Netherlands; [b]Department of Clinical Decision Support, Health Base Foundation, Houten, The Netherlands; [c]Department of Pharmacy, Radboud University Medical Center, Nijmegen, The Netherlands; [d]Centre for Liver Disease Research, Translational Research Institute, Faculty of Medicine, The University of Queensland, Brisbane, Australia; [e]Pharmacy Department, Princess Alexandra Hospital, Brisbane, Australia; [f]Department of Gastroenterology, Radboud University Medical Center, Nijmegen, The Netherlands

ABSTRACT

Introduction: The global burden of cirrhosis is rising, and clinicians increasingly face the challenge of safely prescribing medicines for complications of hepatic disease and comorbidities. Prescribing in patients with cirrhosis is complicated by alterations that can occur in the pharmacology of medicines.
Areas covered: This paper provides an overview of current knowledge on the pharmacokinetics and pharmacodynamics of medicines in patients with cirrhosis. We describe the pathophysiological changes that occur and their consequences on pharmacokinetic parameters. We explain that the influence of cirrhosis on the pharmacokinetics depends on several drug and patient characteristics. Patients with cirrhosis also have an increased susceptibility to some toxicological effects of medicines, such as renal impairment and hematological toxicity, which we describe in detail. In addition, we discuss approaches to apply this knowledge in practice and improve safe medication use in patients with cirrhosis.
Expert opinion: Tailored pharmacotherapy is needed to ensure safe and appropriate use of medicines in patients with cirrhosis. Clinicians are supported by freely available recommendations on safe drug use in cirrhosis published on a website. In addition, a regular evaluation of medication use in patients with cirrhosis could resolve and prevent medication-related problems.

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1. Introduction

Clinicians increasingly face the challenge of safely prescribing medicines in patients with cirrhosis due to the rising burden of chronic liver disease [1]. Over the past decades, the global mortality of cirrhosis has increased to over 1 million deaths annually [2,3]. The most prevalent causes of cirrhosis in Europe are chronic alcohol use disorder, viral hepatitis B (HBV) and C (HCV) infection, and nonalcoholic steatohepatitis (NASH) [4]. All these chronic liver diseases share a similar hepatitis-fibrosis sequence to cirrhosis [5,6]. Regardless of etiology, injury to hepatic tissue can trigger an inflammatory reaction known as hepatitis. Upon progression, scar tissue ensues: fibrosis. While early fibrosis is often asymptomatic, advanced fibrosis or 'cirrhosis' is associated with increasing loss of hepatocyte density and function, formation of scar tissue with regenerative nodules, and intrahepatic resistance to blood flow [5]. This leads to an increase in portal vein pressure followed by the clinical consequences of portal hypertension.

In the clinical setting, cirrhosis in the absence of complications is termed 'compensated.' However, silent progression of portal hypertension and hepatocellular dysfunction can lead to the development of a rapidly progressive 'decompensated' phase, which is characterized by debilitating complications including ascites, hepatic encephalopathy (HE), jaundice, and bleeding [5]. Increasing hepatocyte dysfunction affects several of the metabolic and synthetic functions of the liver [7] including metabolism of endogenous (e.g. bilirubin) and exogenous substances (e.g. medication). Impaired detoxification can lead to accumulation of neurotoxins and contribute to development of HE. Cirrhosis also affects the synthesis of plasma proteins, such as albumin and coagulation factors. Reduced serum albumin and alterations in splanchnic circulation driven by portal hypertension can lead to fluid accumulation in the abdomen (i.e. ascites) [5,7]. Portal hypertension can further result in the development of portosystemic collaterals and esophageal or gastric varices [5,7], which come with a risk of bleeding.

The presence of cirrhosis and its complications can result in clinically important changes in the pharmacokinetics (PK) and pharmacodynamics (PD) of medicines. This can have implications for medication safety as there is an increased risk of adverse drug reactions (ADRs) and patient harm. A cross-sectional study of 400 cirrhotics admitted to a Swiss hospital showed that almost 30%

CONTACT Rianne A. Weersink r.a.weersink@rug.nl Department of Pharmacy, Unit of Pharmacotherapy, Epidemiology and Economics, University of Groningen, Antonius Deusinglaan 1, Groningen 9713 AV, The Netherlands

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Article highlights

- Cirrhosis may affect all pharmacokinetic parameters, which can result in an increased plasma drug concentration. The extent of increase depends on both drug (e.g. pharmacokinetic properties and the administration route) and patient characteristics (e.g. the etiology and severity of cirrhosis).
- Patients with cirrhosis may have an increased susceptibility to the toxicological effects of medicines due to pathophysiological changes.
- Health-care professionals should anticipate these pharmacokinetic and pharmacodynamic changes and can be supported by recommendations for safe prescribing in cirrhosis.

This box summarizes key points contained in the article.

suffered from ADRs [8,9]. Furthermore, of the 210 ADRs noted in this study, the authors judged 78% as probably preventable because of the use of excessively high dosages or contraindicated medicines [9]. To prevent ADRs, patients with cirrhosis should receive pharmacotherapy tailored to the changes in both PK and PD.

This paper provides an overview of current knowledge on the pharmacology (i.e. PK and PD) of medicines in patients with cirrhosis. In addition, we describe approaches to improve safe medication use in patients with cirrhosis in practice and identify areas for further research.

2. Pharmacokinetic changes

Table 1 describes several pathophysiological changes that may occur in cirrhosis and the consequence of these changes on PK parameters [10–13]. These changes could lead to decreased plasma levels of medicines, for example due to diminished prodrug activation or disrupted enterohepatic recycling. However, PK alterations in patients with cirrhosis most frequently result in increased exposure to medicines. The extent of these increases depends on both drug and patient characteristics [14].

2.1. Drug characteristics

The characteristics of a medicine and its route of administration should be taken into consideration when examining the potential impact of altered PK in patients with cirrhosis.

2.1.1. Pharmacokinetic characteristics

As presented in Table 1, all PK parameters may be affected by cirrhosis. To explain the outcome of these changes on drug plasma levels, the well-stirred model is frequently used [11,13,14]. This model assumes that hepatic drug clearance depends on three factors: (1) hepatic blood flow, (2) the hepatocytes' ability to metabolize a medicine (intrahepatic clearance), and (3) the fraction of unbound medicine [11,13,14]. The hepatic extraction ratio (E_H) is the fraction of drug cleared from the blood during a single passage through the liver. In the well-stirred model, medicines are classified by their hepatic extraction ratio into: high (E_H>0.7), intermediate (E_H: 0.3–07), and low (E_H<0.3) extraction drugs [11].

For drugs with a high E_H, the liver is very efficient in clearing the medicine from the blood. Therefore, hepatic blood flow is the factor limiting hepatic clearance ('flow-limited'). These medicines usually undergo substantial first-pass metabolism when orally administered in healthy patients [13]. However, in patients with cirrhosis, pathophysiological changes that affect blood flow, such as the development of portosystemic shunts, can have a large influence on circulating drug plasma levels. An example of this is the medicine naltrexone, which has a bioavailability of 5–40% in healthy individuals. Exposure to naltrexone is approximately fivefold higher in compensated, and tenfold higher in decompensated cirrhosis, compared to healthy controls [15], likely explained by a diminished first-pass effect.

For drugs with a low E_H, the liver is less efficient in clearing medicines from the blood. Therefore, drug clearance is predominantly influenced by intrinsic hepatic clearance and the free fraction of the medicine ('capacity-limited'). These medicines are sensitive to changes in plasma protein binding (if highly protein bound) and reduced metabolic enzyme activity. Examples of low E_H medicines include proton pump inhibitors (PPIs), lansoprazole and pantoprazole. Exposure to both medicines is largely increased in patients with cirrhosis, which results from a decrease of CYP2C19 enzyme activity in cirrhosis [16].

At last, the hepatic clearance of medicines with an intermediate E_H depends on all the three factors (i.e. hepatic blood flow, hepatic metabolic activity and fraction of unbound medicine). An example of such a medicine is paroxetine. In patients with cirrhosis, a doubled exposure to paroxetine has been seen after multiple-dosing [17].

Gonzales and colleagues used data from 84 published pharmacokinetic studies to describe the relationship between certain drug characteristics (including E_H) and the extent of PK alterations in patients with cirrhosis [18]. In subjects with moderate and severe hepatic impairment, a trend toward a higher exposure to medicines with higher E_H ratios was found. However, the clinical meaning of this finding is uncertain as some medicines with a low E_H also exhibited major increases in exposure. The only significant negative predictor for large PK alterations was extensive renal elimination. If more than 40% of a medicine was excreted unchanged in the urine, the predicted increase in exposure was less than twofold. Yet, this finding should be interpreted with caution since patients with severe cirrhosis may also suffer from (covert) renal impairment [11]. Furthermore, the administration route of the study drugs was not considered as a variable, which may also influence the extent of PK changes in cirrhosis.

2.1.2. Route of administration

As a result of hemodynamic changes in cirrhosis, portosystemic shunts may develop. The consequence is that medicines may be less exposed to the first-pass effect of the liver and drug bioavailability can substantially increase. All administration routes that are subjected to the first-pass effect can be impacted, with the greatest effect on medicines with a high E_H.

The difference in PK changes between oral and parental administration in cirrhosis has been demonstrated for several medicines. Coting and colleagues [19] found a fourfold greater exposure to isradipine following oral administration, and a twofold increase following intravenous administration in patients with cirrhosis versus healthy controls, respectively. The biological availability of oral isradipine increased from 17% in healthy patients to 37% in the patients with cirrhosis

Table 1. Overview of pathophysiological abnormalities that can occur in patients with cirrhosis and the consequences on pharmacokinetic parameters.

	Pathophysiological change	Pharmacokinetic change
Absorption	• Portal hypertensive gastropathy, ulcers of the upper gastrointestinal tract, gastritis • Increased intestinal permeability • Impaired gastrointestinal motility with delayed gastric emptying	• Altered extent of drug absorption • Decreased rate of absorption
	• Altered hepatic blood flow (e.g. portosystemic shunts, TIPS) • Reduced intrinsic clearance	• Decreased first-pass effect resulting in a higher bioavailability • Pro-drug metabolism diminished
Distribution	• Decreased levels of plasma proteins (e.g. albumin, α_1-acid glycoprotein) due to impaired synthesis in the liver • Accumulation of endogenous substances, such as bilirubin, displacing binding sites of plasma proteins • Fluid retention (ascites, edema)	• Reduced plasma protein binding resulting in a larger fraction of unbound drug • Enlarged volume of distribution
Metabolism	• Alterations in hepatic architecture including hepatocellular necrosis, altered blood flow, and nodular formation	• Reduced activity or expression of phase I and II drug-metabolizing enzymes (reduced intrinsic clearance). The extent of reduced activity differs per enzyme. Some enzymes are very sensitive for these pathophysiological changes (e.g. CYP2C19), while others are affected in a later stage (e.g. CYP2D6). • Changes in stereoselectivity of hepatic drug metabolism
	• Reduced blood flow across the liver	• Delayed clearance by drug-metabolizing enzymes
Elimination	• Bile flow obstruction, due to cancer or sclerosing cholangitis • Reduced protein transporter expression	• Biliary excretion reduced • Disrupted enterohepatic recycling
	• In advanced cirrhosis, renal impairment	• Reduced renal elimination

TIPS: transjugular intrahepatic portosystemic shunt

[19]. Increased bioavailability has also been demonstrated with nifedipine, an intermediate E_H drug. Kleinbloesem and colleagues showed oral bioavailability was around 50% in healthy controls and increased to 90% in patients with cirrhosis [20]. Exposure to oral naltrexone also increases substantially in cirrhosis (fivefold and tenfold increase in patients with compensated and decompensated cirrhosis, respectively) compared to healthy controls [15]. After intramuscular injection, the pharmacokinetics of naltrexone in patients with mild and moderate cirrhosis was not different from that of healthy controls [21], although data in patients with severe cirrhosis is lacking.

Theoretically, an increase in bioavailability following rectal administration could also occur, yet no pharmacokinetic studies could be found that examined this.

2.2. Patient characteristics

Characteristics of people with cirrhosis can further influence the PK changes that occur [14]. Such patient characteristics include the severity of cirrhosis, the presence of a transjugular intrahepatic portosystemic shunt (TIPS) and (possibly) the type of underlying liver disease. In addition, some other characteristics such as nutritional status and genetic polymorphisms may also impact the PK changes that occur.

2.2.1. Severity of cirrhosis

Progression of the underlying liver disease can lead to deterioration of liver function and progression of cirrhosis complications, which can further influence PK changes. For example, a (differential) decline in the activity of almost all metabolizing enzymes has been demonstrated with increasing severity of cirrhosis [10,11]. This often results in increased drug plasma levels and greater exposure to medicines [22–26]. Additionally, with increasing severity of cirrhosis, renal function frequently also declines [5].

To assess the severity and prognosis of cirrhosis, the Child–(Turcotte)–Pugh classification is commonly used in clinical practice [27,28]. Registration authorities also demand to use the Child-Pugh classification for categorizing patients by severity of hepatic dysfunction in pharmacokinetic studies with new medicines [29,30]. That is why product labels

commonly provide dosing recommendations based on Child-Pugh class [31]. However, the Child-Pugh classification was not developed for this purpose and appropriate use of the score in clinical practice is essential to enable interpretation. For example, the Child-Pugh classification should not be used to screen for hepatic impairment, as individual parameters are not specific for hepatic dysfunction. Bilirubin can be increased due to hemolysis or Gilbert's syndrome, and albumin decreased due to sepsis [27]. In addition, if the Child-Pugh score is calculated in persons without cirrhosis they will all be categorized as 'mild hepatic impairment' because that is the minimum score [27].

In older literature, often no distinction was made in the severity of cirrhosis of the participants, which could have affected the PK changes that were found. For example, in a study from 1993, fluvoxamine was administered to 13 patients with cirrhosis, not specified by severity. An increase in exposure of 50% in the patients with cirrhosis was found compared to healthy controls [32]. Comparatively, a more recent work that studied both patients with Child–Pugh A cirrhosis and Child-Pugh C cirrhosis demonstrated an exposure increase of 50% and 150%, respectively, compared to healthy controls [24].

2.2.2. TIPS

If the complications of portal hypertension get too severe (e.g. refractory ascites, recurrent or uncontrolled variceal bleeding), a TIPS could be placed to decrease portal pressure by connecting the portal vein to the hepatic vein [6,7]. This can particularly affect the first-pass metabolism, yet the influence of TIPS on PK has only been limitedly studied. A study with midazolam demonstrated that in patients with cirrhosis and a TIPS, plasma levels after oral administration were 1.5 times higher than in cirrhosis without a TIPS [33]. In addition, a case-report described the toxicity of beta-blockers and diltiazem after TIPS placement [34]. All these medicines have a high or intermediate E_H and are therefore sensitive to changes in blood flow caused by TIPS. On the other hand, in a patient with Child–Pugh A cirrhosis, only a minor elevation in peak plasma levels of caspofungin was noted after TIPS placement [35], comparable to Child–Pugh A patients without a TIPS. It has been estimated that caspofungin has a low E_H [18]. Hence, TIPS placement will likely have a greater influence on the plasma levels of orally administered medicines with high and intermediate E_H.

2.2.3. Etiology of cirrhosis

The underlying type of hepatic disease could potentially affect the extent of PK changes via altered expression and activity of drug-metabolizing enzymes. One study documented that the cause of cirrhosis (hepatocellular or cholestatic) results in differences in CYP-enzyme expression [36]. A recent article by Prasad and colleagues assessed the abundance of metabolic enzymes in livers from transplanted patients with Child-Pugh C cirrhosis caused by alcohol versus HCV. In general, the abundance of most enzymes in cirrhotics is reduced to 25–50% compared to healthy livers [37]. In particular, cirrhotic livers affected by alcohol have profoundly lower alcohol dehydrogenase 1A and 1B and UGT1A4 compared to cirrhosis caused by chronic hepatitis C [37].

Studies have compared the actual effect of different etiologies of cirrhosis on drug plasma levels and clearance of substances. In a work by Breimer and colleagues [14], clearance of antipyrine (low E_H) was compared between groups of patients with different underlying causes and severity of the liver disease. Patients with alcoholic cirrhosis had the lowest clearance, yet overlap existed with the group of patients with a primary biliary cirrhosis, those with cryptogenic cirrhosis and those with chronic active hepatitis. A study with the bile acid glycocholic acid (high E_H) compared clearance between groups of patients with acute hepatitis (viral/alcoholic), chronic viral hepatitis, alcoholic/cryptogenic cirrhosis, primary biliary cirrhosis and healthy controls [38]. Clearance in the two cirrhosis groups was significantly decreased compared to controls and the hepatitis groups, but no differences between the groups with cirrhosis were found. The presence of jaundice was an important confounder, most likely reflecting the severity of hepatic impairment. Therefore, while the expression and activity of enzymes may differ between types of liver disease underlying cirrhosis, the clinical implications of altered plasma drug levels are uncertain.

2.2.4. Other patient characteristics

There are also other patient characteristics that may influence the pharmacokinetics of medicines in patients with cirrhosis, such as nutritional status and genetic polymorphisms. Cirrhotic patients are often malnourished [6], especially in decompensated cirrhosis and this may affect paracetamol pharmacokinetics [39,40]. A small proportion of paracetamol is metabolized by CYP2E1 to the hepatotoxic intermediate N-acetyl-p-benzoquinone imine (NAPQI). Glutathione detoxifies NAPQI. Malnourishment may lead to lower glutathione levels and theoretically a higher risk of hepatotoxicity [39,41]. Yet, in patients with cirrhosis, the outcome is difficult to predict because CYP2E1 activity is possibly already decreased with less NAPQI formed. In addition, another factor that may affect paracetamol pharmacokinetics is (chronic) use of alcohol. This can induce CYP2E1 and consequently NAPQI formation [39]; however, this has not been demonstrated in cirrhotic patients [41].

Genetic polymorphisms affect the activity of drug-metabolizing enzymes. There is a paucity of data on the combined influence of cirrhosis and genetic polymorphism on medicine clearance. The most comprehensive study was performed by Ohnishi and colleagues and compared CYP2C19 activity in healthy controls and patients with cirrhosis using the omeprazole hydroxylation index [42]. They found that CYP2C19 activity in healthy controls with a poor metabolizer (PM) genotype was comparable to the CYP2C19 activity of cirrhotic patients with a heterozygous and homozygous extensive metabolizer genotype. The hydroxylation index of patients with a PM genotype was significantly higher than these groups, suggestive of an even lower CYP2C19 activity. Another study demonstrated that exposure to pantoprazole in patients with Child-Pugh B and C cirrhosis was comparable to healthy controls that were PM of CYP2C19 [43]. The authors did not determine the genotype

of cirrhotic patients. Two articles assessed the influence of CYP2D6 polymorphism on the hemodynamic effect of propranolol in patients with cirrhosis [44,45]. The study by Zhang and colleagues [45] found that a specific CYP2D6 genotype (188C>T) was a predicting factor for hemodynamic response to propranolol, while the other article did not find a polymorphism related to response [44]. Both studies did not compare their results to a control group of subjects without cirrhosis.

3. Pharmacodynamic changes

Patients with cirrhosis may respond differently to the same medicine plasma concentrations as healthy persons. This is explained by changes in the number and sensitivity of receptors or the access of medicine to the site of action. This could result in a diminished or more pronounced therapeutic effect, including potential toxicity in patients with cirrhosis.

3.1. Altered pharmacological effect

There is a paucity in the literature on changes in the therapeutic effect of medicines in patients with cirrhosis. Most research to date has focussed on diuretics, beta-blockers, muscle relaxants, and renin-angiotensin-aldosterone system (RAAS) inhibitors. A diminished response to diuretics such as furosemide and torsemide, independent of PK changes, has been demonstrated [46–49]. This could be related to reduced diuretic potential of the nephrons and/or a reduced number of nephrons [46]. After a single dose of the beta-blocker metipranolol, a less pronounced effect on heart rate was demonstrated in patients with cirrhosis compared to healthy controls [50]. The authors suggest that due to chronic sympathetic activation, downregulation of beta-adrenoreceptors could occur [50]. However, a recent study revealed that the response to propranolol was dose-dependent and not different to healthy controls when controlled for the PK alterations that occur in cirrhosis [51]. The effect of cirrhosis on the response to muscle relaxants has been relatively well studied [52–59]. All these studies demonstrated that if differences occurred in pharmacological response, these were correlated with differences in PK parameters. Therefore, sensitivity to the effect of muscle relaxants seems to be comparable to healthy controls.

The evidence on the pharmacological response to RAAS-inhibitors in patients with cirrhosis is conflicting. Several studies demonstrated that the percentage of angiotensin-converting enzyme (ACE) inhibition in cirrhosis was not different than in healthy controls [60–63]. One found a largely decreased activation of enalapril to its active form in patients with cirrhosis, yet the effect on blood pressure was similar to the healthy controls suggesting that the patients are more sensitive to this effect [61].

3.2. Altered toxicological effect

Patients with cirrhosis could have an increased susceptibility to the toxicological effects of medicines. Croxen and colleagues previously published a comprehensive overview of undesirable side effects in patients with liver disease [64]. Figure 1 provides an overview of the pathophysiological changes in cirrhosis that may contribute to an increased risk of ADRs in patients with cirrhosis.

3.2.1. Renal impairment

Studies involving nonsteroidal anti-inflammatory drugs (NSAIDs) [65,66] demonstrated a significant decrease in the mean glomerular filtration rate of around 30% in patients with cirrhosis following the use of a NSAID. In another paper, 50%

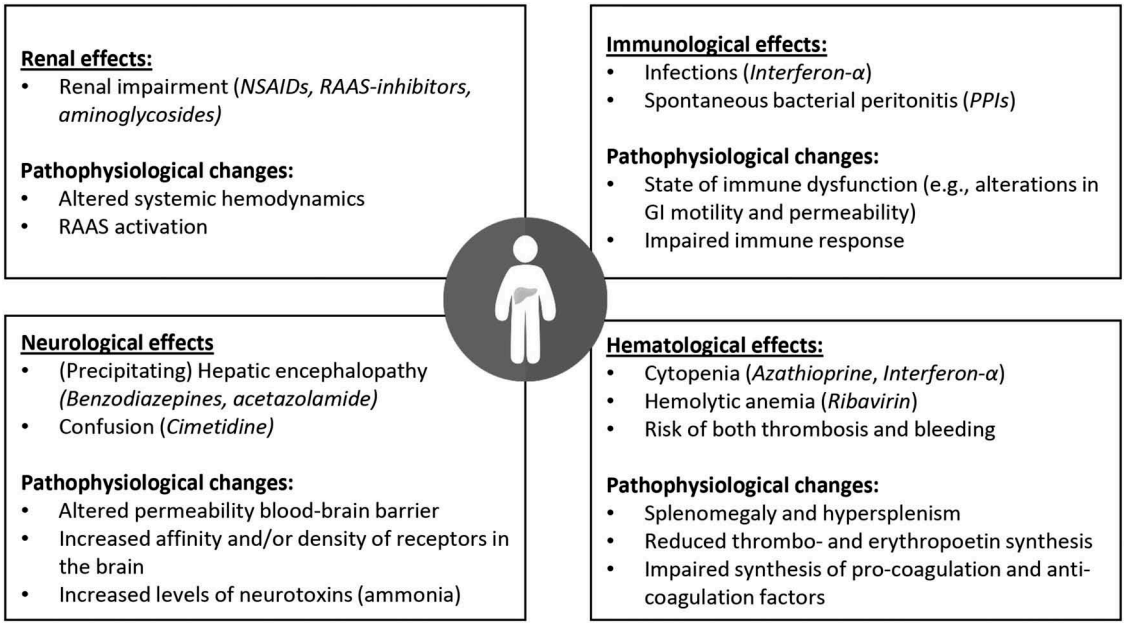

Figure 1. Overview of toxicological effects that patients with cirrhosis seem to be more susceptible to compared to healthy controls and underlying pathophysiological changes.

ADR: adverse drug reaction, GI: gastro-intestinal, PPIs: proton pump inhibitors, NSAIDS: non-steroidal anti-inflammatory drugs, RAAS: renin-angiotensin-aldosterone system

of patients with cirrhosis using ibuprofen-developed renal impairment [67]. RAAS-inhibitor use has also been linked to the development of renal dysfunction in patients with decompensated cirrhosis [68]. In 18 patients with a history of ascites, 4 (22%) suffered from (transient) renal impairment after irbesartan use [69]. There are several ways in which medicines can induce renal impairment in patients with cirrhosis.

Cirrhosis-driven interference with renal hemodynamics has been well described [70]. Alteration in systemic hemodynamics occurs in patients with cirrhosis as progressive portal hypertension causes splanchnic vasodilation. To preserve renal function, the RAAS system is activated leading to excretion of renal vasodilators for the afferent arterioles (e.g. prostaglandins) and vasoconstrictors for the efferent arterioles (e.g. angiotensin-II (AT-II)) [71]. Medicines that interfere with this mechanism, such as RAAS-inhibitors and NSAIDs (by inhibiting AT-II and prostaglandin synthesis, respectively) could lead to acute renal impairment [70].

Another mechanism by which medicines may induce renal impairment is by a direct toxic effect on tubular cells [70]. Of note, these cells are also involved in the metabolism of prostaglandins [70,72]. Aminoglycosides are medicines that cause nephrotoxicity by this mechanism, and renal impairment was more frequent in patients with underlying liver dysfunction compared to healthy controls or patients receiving a different antibiotic [72,73]. Both studies described four to five times higher odds for developing aminoglycoside-associated renal impairment among patients with preexisting hepatic dysfunction. It is unknown whether this was caused by tubular toxicity, interference with prostaglandin metabolism, or a synergistic toxic effect.

3.2.2. Neurotoxicity

Another well-known risk in patients with cirrhosis is the potential for neurotoxicity (e.g. confusion, HE) with certain medicines. A recent work by Bajaj and colleagues demonstrated the significant role of medicines in precipitating HE [74]. Among 2810 patients with cirrhosis, 5% of the 913 HE episodes were related to benzodiazepines, 4% to opioids and 1% to hypnotics. Similarly, another study showed that benzodiazepine use for 3 to 10 days increased the risk of developing HE by fivefold [75]. A number of pathophysiological mechanisms for neurotoxicity have been proposed: (1) a higher permeability of the blood-brain barrier (BBB), (2) an increased density or affinity of certain receptors in the brain, and (3) an increase in circulating neurotoxins such as ammonia.

The theory of increased BBB permeability is supported by a recent study by Weiss and colleagues, in which several drugs and metabolites were found in the cerebrospinal fluid (CSF) of 14 patients with HE that were not present in the CSF of controls [76]. Indeed, a doubled CSF to serum ratio of cimetidine is seen in cirrhosis [77]. Both results suggest that medicines accumulate in the brain. The reason for the increased BBB permeability is not well understood. It has been suggested that high exposure to bilirubin results in down-regulated or occupied efflux pumps (i.e. P-glycoprotein and multi-drug-resistance protein-1) [76].

With regard to the receptor theory, at comparable (unbound) plasma levels of benzodiazepines, excessive sedation was noted in cirrhotics compared to controls [78–80]. Benzodiazepine levels in the CSF were not higher than those in controls [81]. Another study demonstrated an increased density of one type of benzodiazepine receptor ('peripheral-type') in the brain of deceased patients with HE [82]. The receptor binds, amongst others, benzodiazepine-like drugs. The upregulation is possibly induced by inflammation [83]. Activation leads to the synthesis of neurosteroids that can modulate the gamma-aminobutyric acid (GABA) receptor system, and has been linked to the pathogenesis of HE [83].

A third possible mechanism for neurotoxicity in cirrhosis is the medicine-induced increase of neurotoxins. It has been demonstrated that certain substances (e.g. ammonia, lactate, and manganese) are toxic for the brain [84]. Higher levels of these neurotoxins due to medicine use could contribute to HE. For example, acetazolamide increases the excretion of bicarbonate in the urine, thereby decreasing ammonia excretion. Several studies describe HE occurrence in patients with cirrhosis using acetazolamide that is not explained by the progression of the underlying disease [85–87]. This mechanism may further contribute to the impaired BBB theory, as ammonia can only cross this barrier at high levels [88]. In addition, ammonia can contribute to neuroinflammation [84], thereby possibly also affecting neuroreceptors. This example demonstrates that the mechanism underlying the neurotoxicity of medicines in patients with cirrhosis is probably multifactorial and requires further research.

3.2.3. Immunological effects

Patients with cirrhosis are often in a state of immune dysfunction due to a number of factors (e.g. increased mucosal permeability of the gastrointestinal tract, reduced activity of hepatic reticuloendothelial cells) [89,90]. Immunosuppressive therapy (such as interferon-α) may exacerbate this state. Indeed, a higher prevalence of infections has been noted in cirrhotic patients on interferon-α therapy compared to healthy controls [91,92]. In one of these studies, 3 of 26 patients (12%) developed a severe infection [91] and in the other, 9 patients (28%) developed a bacterial infection after interferon-α therapy [92]. PPIs have also been associated with an increased risk of infections and spontaneous bacterial peritonitis in patients with cirrhosis [16]. This effect is likely driven by the increase in gastric pH, which could lead to bacterial colonization, overgrowth, and translocation [93].

3.2.4. Hematological effects

Due to their disease, patients with cirrhosis frequently have alterations in baseline hematological parameters. Portal hypertension can lead to hypersplenism and a lower platelet count [94,95], and hepatic impairment is associated with reduced synthesis of hematopoietic growth factors (thrombopoietin and erythropoietin) and coagulation factors (procoagulants and anticoagulants) [96,97]. One study has also indicated that patients with cirrhosis lack the appropriate compensatory increase in thrombopoietin in response to thrombocytopenia [98].

Several medicines (e.g. azathioprine, interferon-α, ribavirin) have been linked to hematotoxicity in patients with cirrhosis. Two studies have demonstrated that the risk of

(hematological) toxicity with azathioprine is significantly increased in cirrhosis [99,100]. In one of these, 75% of 61 patients with cirrhosis developed cytopenia compared to 33% of 114 non-cirrhotic patients [100]. The other was a case–control study among 86 patients with autoimmune hepatitis of which 26% suffered from azathioprine toxicity and 74% did not [99]. In the first group, 55% of patients had underlying cirrhosis, while this was only 30% of patients in the second group. Of note, azathioprine is also metabolized by the liver and PK could therefore also alter in cirrhosis [101]. Interferon-α could also provoke mild bone marrow suppression and in patients with cirrhosis, decreases in platelets and leukocytes were more marked compared to patients without cirrhosis [102]. In a randomized trial of 60 patients with viral hepatitis treated with interferon-α, 22% of the 23 patients with cirrhosis developed neutropenia or thrombocytopenia, whereas only 5% of 37 patients without cirrhosis developed cytopenias [103]. In another study, 7 (58%) of 12 patients with chronic viral hepatitis and cirrhosis developed neutropenia or thrombocytopenia, compared to only 1 (13%) of the 8 patients without cirrhosis [104].

Ribavirin is also known for inducing hemolytic anemia. A study among 244 patients with HCV showed that patients with a lower baseline platelet count experienced a significantly greater drop in hemoglobin levels [105]. The 29 patients with Child–Pugh A cirrhosis in the study had a significantly lower baseline platelet count compared to the 215 patients without cirrhosis. The authors describe that not per se the histological diagnosis of cirrhosis, but its clinical expression puts patients at risk for more severe ribavirin-induced hemolytic anemia [105]. To sum up, patients with cirrhosis often have alterations in hematological parameters before treatment. This pathophysiologic state could increase the risk of (severe) hematological toxicity.

The effect of medicines on coagulation in cirrhosis is complex. The hemostatic balance in patients with cirrhosis is very fragile, partly due to impaired hepatic synthesis of pro- and anti-coagulation factors [96]. Therefore, patients with cirrhosis are at risk for both bleeding and thrombotic events [96]. Anticoagulant therapy is further challenged by the large involvement of the liver in the PK of these medicines. In addition, regular laboratory parameters to monitor the safety and efficacy of therapy (e.g. INR) are often deranged at baseline due to the changes highlighted above. Overall, anticoagulation therapy is complex and challenging in patients with cirrhosis and much is still unknown [96].

3.2.5. Hepatotoxicity

Hepatotoxic effects are not included in Figure 1, because it has long been assumed that patients with underlying liver disease are not at an increased risk to experience idiosyncratic drug-induced liver injury (DILI) compared to healthy patients [106]. It was also assumed that if DILI did occur in these patients, the consequences would be more severe than in patients without underlying liver disease [106].

This last assumption was recently confirmed in a prospective study with data from the United States DILI network [107]. The mortality rate in patients with underlying liver disease suffering from DILI (n = 89) was significantly higher compared to patients without underlying liver disease (n = 810; 16% versus 5.2%). Remarkably, this study also found that the incidence of azithromycin DILI was higher in patients with underlying liver disease (6.7% versus 1.5%), which is in contrast to the first assumption that these patients do not have an increased risk of DILI. The authors recommended that further research is needed because their result could also be explained by a higher usage of azithromycin in this patient population.

The greatest difficulty in research on DILI in patients with underlying liver disease is the distinction between additional liver injury caused by a medicine or progression of the underlying liver disease. In addition, some medicines used for treating liver diseases have been linked to additional liver injury, such as some antiviral treatments used for hepatitis C and obeticholic acid, used in the treatment of primary biliary cholangitis [108,109]. In these cases, causality is very difficult to determine. With regard to HCV treatment, another factor is possibly involved: a paradoxical response of the liver to virus clearance [110]. For obeticholic acid, the FDA issued a warning that several incidents of liver injury and some deaths have been reported with the use of obeticholic acid in patients with Child-Pugh B and C cirrhosis [108]. However, this was probably explained by inadequate prescribing: instead of the once-weekly dosing in patients with Child-Pugh B and C cirrhosis, patients were treated with the 'regular' once-daily dose [111].

4. Conclusion

Management of patients with cirrhosis is complicated by alterations in the pharmacology of many medicines that are indicated for the treatment of liver disease and comorbidities. The influence of cirrhosis on the PK of a drug depends on both drug and patient characteristics. Patients with cirrhosis can exhibit different pharmacological and toxicological responses to the same drug plasma concentrations compared to patients without cirrhosis due to pathophysiological changes. Tailored pharmacotherapy is needed to ensure the safe and appropriate use of medicines in this vulnerable patient group.

5. Expert opinion

The changes in the pharmacology of medicines need to be considered when prescribing in cirrhosis. Patients with cirrhosis often present a complex clinical picture and pharmacotherapy in these patients can, therefore, be challenging. In this part, we discuss approaches to implement the knowledge of PK and PD changes into clinical practice. In addition, we describe topics for further research.

5.1. Use guidance for prescribing in patients with cirrhosis

There has been limited guidance to support safe prescribing in cirrhosis in the past. Advice from the product label about dosing in hepatic impairment was often unclear, inconsistent, and recommendations were not specified by the severity of impairment [112–114]. Several research groups have attempted to provide health-care professionals with more

Table 2. Safety and dosing recommendations for the use of zolpidem and zopiclone in patients with cirrhosis, based on the method by Weersink et al. [119] and retrieved from www.drugsinlivercirrhosis.org.

Zolpidem	
Safety class	Unsafe (recommended action: avoid the use)
Dosing advice	No dosing advice (unsafe)
Evidence: one pharmacokinetic study was retrieved in six patients with cirrhosis (severity unknown) partly described in a pharmacokinetic review [121] and in the FDA label [122]. The peak plasma levels were doubled in patients with cirrhosis compared to healthy controls and half-life prolonged to 10 hours (2 hours in controls). The total exposure was fivefold higher in patients with cirrhosis. Regarding safety, we retrieved data on six cases of hepatic encephalopathy associated with zolpidem identified by the FDA [123], two were described in a case report [124,125]. In a cross-sectional study six more cirrhotic patients had mental deterioration while using zolpidem [9]. Because of the large pharmacokinetic alterations, the risk of hepatic encephalopathy and the availability of safer alternatives, zolpidem is classified as 'unsafe' in patients with cirrhosis. This is in contrast to the advice from the product information, which only advises to use one-half of the normal dosage [122].	
Zopiclone	
Safety class	Additional risks known (recommended action: use a safer alternative if available)
Dosing advice	Child-Pugh A: start at the lower end of the dosing range Child-Pugh B: start with half of the normal dose Child-Pugh C: no dosing advice possible
Evidence: Two studies explored the pharmacokinetics of a single-dose of oral zopiclone in 17 patients with cirrhosis (severity unknown) [126,127]. Bioavailability increased by 20% in patients with cirrhosis, but peak plasma level were comparable to healthy controls. Half-life was prolonged to 8.5 hours in the two studies (3.5–5 hours in controls). The exposure to zopiclone was increased by 43% in patients. One of the studies found a negative correlation between serum albumin and elimination half-life. The pharmacodynamic response was measured in one of these study and psychometric tests were more impaired in cirrhotics than in controls [126]. Zopiclone is classified as 'additional risks known' based on the risk of hepatic encephalopathy. The authors of one study and the product information advise to start with one-half of the normal dose, i.e. 3.75 mg per day [127]. It is recommend to start at the lower end of the normal dosing range in Child-Pugh A and to start with half of the normal dose in Child-Pugh B. In patients with Child-Pugh C no data is available and no dosing advice could be given.	

support by publishing reviews on the use of certain medicines (groups) in cirrhosis [115–118]; however, most remained vague in their advice (e.g. 'use with caution' or 'dose adjustment needed') and recommendations were not updated.

To address this lack of guidance, a research project was started in 2015 to develop freely available medication safety and dosing recommendations for medicines in patients with cirrhosis [119]. Data on the safety and pharmacokinetics of medicines in patients with cirrhosis were collected from the literature and product labels. Available evidence was reviewed by a panel of experts, leading to the formation of safety advice (e.g. can be used, use a safer alternative if possible, or avoid the use) and dosing advice for 218 medicines (including consideration of the severity of cirrhosis [28]). The safety advice was based on evidence of additional harm in patients with cirrhosis compared to healthy controls. Dose adjustments were generally recommended if the exposure was more than doubled, thereby considering the therapeutic window of the drug. In Table 2, an example of the evaluation of non-benzodiazepine drugs for insomnia (zolpidem and zopiclone) is provided. In total, over 200 recommendations were developed and published in an open access article in 2018 [120]. In this article, all the safety recommendations can be found with dosing advice, if applicable. Of the 218 medicines, 31% were classified as unsafe in (a stage of) cirrhosis and also for 31% of medicines a dose adjustment was advised [120]. The recommendations were also published on a free Dutch website: www.geneesmiddelenbijlevercirrose.nl (English example of this website: www.drugsinlivercirrhosis.org) and integrated into primary care clinical decision support systems (CDSS) in the Netherlands. Currently, almost 300 recommendations for safe medication use in patients with cirrhosis have been developed. In supplementary Table 1, an overview is provided of the most important recommendations for clinical practice.

These recommendations could be useful when prescribing in patients with cirrhosis, especially to assist non-gastroenterologists. This is an evolving space, and new research will be vital to continue developing new recommendations to support the safe prescribing of many more medications and to reinforce the evidence base of current recommendations. In practice, precaution is needed when prescribing medicines for which there is currently limited advice, especially in people with severe cirrhosis (Child-Pugh C), as these patients are at greatest risk for ADRs associated with changes in PK and PD. Furthermore, clinical indication in some circumstances may outweigh risks of treatment, and the presence of comorbidities may also influence treatment choice and dosage. This should be assessed on a case-by-case basis.

5.2. Regularly evaluate pharmacotherapy

The appropriateness and safety of medications can change with the progression of liver disease, development of new complications and/or comorbidities over time. A recent Australian study in a cohort of people with decompensated cirrhosis identified a median of six medication-related problems per patient (range 2–17) [128]. Almost half of these problems were judged to be 'high' risk for potential harm to the patient. Examples of problems included nonadherence (patient-driven due to ADRs), and drug–drug and drug–disease interactions (often relating to risk of renal impairment or HE). These are common problems among patients with cirrhosis [128–132]. The patient-oriented medication intervention described in the trial was associated with a reduced incidence rate of unplanned hospital admissions compared to usual care, which coincided with 68.9% resolution rate of 'high' risk medication-related problems [128]. This study demonstrated that it is important to regularly reevaluate pharmacotherapy in patients with cirrhosis after prescribing to ensure the ongoing safe and appropriate use of medications. Multidisciplinary medication reviews, as often done in older patients, may be a good model to be followed for this patient group as well [133]. The implementation of prescribing information in clinical decision support systems as highlighted above supports such efforts.

5.3. Further research topics

There are still important gaps in knowledge on the safety and optimal dose of certain medicines in patients with cirrhosis. More research is needed on both PK and PD alterations. The list of medicines classified as having 'unknown' safety in (a stage of) cirrhosis could be used to prioritize this research [120]. The primary information about alterations in the pharmacology of medicines in patients with cirrhosis originates from the pre-marketing PK studies conducted by the pharmaceutical industry. In a recent article, we demonstrated that a large proportion of product labels from recently authorized medicines contained information on use in hepatic impairment patients [134]. However, we also showed that this information was frequently ambiguously formulated and therefore not per se clinically applicable.

The studies conducted for market authorization concentrate on PK, as is also the focus of the regulatory guidelines [29,30]. Both guidelines do acknowledge that the effect of medicines could also be different in hepatic impairment and advise to include efficacy and safety endpoints in the PK studies when possible [29,30]. Yet, this is limited by the common design of these PK studies: a small number of patients (usually around six per severity class and often no patients with severe cirrhosis) and only a single dose of the study drug is administered [134]. Toxicological effects could be hard to detect because of a low frequency or because they resemble the natural course of cirrhosis [135]. As a result, it is likely that alterations in the effects are not yet revealed during these pre-marketing studies. Larger studies with a longer follow-up are needed, which are usually performed in the post-marketing setting.

In this post-marketing phase, experimental research is warranted (e.g. PK studies and randomized controlled trials). However, performing these studies is complicated by difficulties in recruiting enough relatively healthy cirrhosis subjects and by ethical concerns of research in such a patient group (especially in people with Child-Pugh C cirrhosis) [11]. As such, post-marketing information mostly results from clinical practice (e.g. spontaneous reporting, case-reports and case-series) and observational research. In particular for these types of research, a few things are important to consider. Firstly, when evaluating additional medication harm in patients with cirrhosis, two questions are specifically relevant: (1) is the noticed effect an ADR or a complication of cirrhosis? and (2) is the effect more common in patients with cirrhosis than in healthy controls? To best answer these questions, a control group of patients with cirrhosis and one of the healthy controls is desired. Secondly, it is also important to discriminate between medication harm due to an overdose (PK alterations) or due to an increased susceptibility (PD alterations). For example, in a study among patients with severe hepatic dysfunction, a higher frequency of leukopenia occurred in patients that used β-lactam antibiotics, compared to patients using other antibiotics [136]. The authors reported that this was probably caused by excessive serum concentrations, although these were not measured, and proposed dose reductions for β-lactam antibiotics in these patients. However, as previously discussed, patients with cirrhosis can be more susceptible to hematotoxicity. As efficacy is essential for antibiotics, dose adjustment should only be advised when PK data (i.e. (unbound) plasma levels) are available. Lastly, it would be very helpful for clinical practice to gain more knowledge on the prevalence, risk factors and outcome of ADRs in patients with cirrhosis to better support their clinical decision-making for the vulnerable patient with cirrhosis.

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ORCID

Rianne A. Weersink http://orcid.org/0000-0001-6996-894X

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