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REVIEW ARTICLE

Management of Pharmacologic Adverse Effects in Advanced Liver Disease

Miren García-Cortés[1,2] · **Alberto García-García**[1]

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Abstract

As a consequence of the altered hepatic architecture in advanced liver disease, drug metabolism is modified by changes in pharmacokinetic and pharmacodynamic properties, leading to the appearance of adverse effects and drug interactions and increasing the risk of over- or underdosing of medications. However, there are no tests that accurately determine the degree of impairment of liver metabolic function; therefore, general recommendations are established based on the degree of hepatic extraction, degree of hepatic metabolism, and degree of protein binding. Although the hepatic toxicity of some frequently used drugs, such as acetaminophen, is well known, many health care professionals are unaware or not fully aware of the deleterious effects that other drugs can have on patients with advanced liver injury, as is the case for nonsteroidal anti-inflammatory drugs. It is very important to increase awareness among both health care professionals and patients with advanced liver disease to limit the use of inappropriate drugs and prevent drug-induced liver injury.

Key Points

The loss of normal liver architecture in advanced liver disease changes pharmacodynamic and pharmacokinetic properties of the drugs, increasing the risk of interactions and adverse events.

There is no method for assessing the degree of impairment of liver metabolic function, so general recommendations are established based on the degree of hepatic extraction, hepatic metabolism, and protein binding.

Although many of the adverse events of the drugs prescribed to patients with liver disease are preventable and controllable, patients are at a higher risk of developing some forms of pharmacologic hepatotoxicity.

✉ Miren García-Cortés
mirengar1@hotmail.com

[1] Unidad de Gestión del Aparato Digestivo, Hospital Universitario Virgen de la Victoria, Málaga, Spain

[2] Universidad de Málaga, IBIMA, CIBERehd, Málaga, Spain

1 Introduction

Alterations in hepatic architecture in advanced liver disease lead to a progressive deterioration of liver function, including changes in the metabolism of drugs and toxic substances. As a consequence, adverse effects may appear, pharmacologic interactions may occur, and the risk of supra- or infradosification may increase [1].

Pharmacokinetic changes in patients with advanced liver disease can occur due to alterations in different phases of drug metabolism, such as absorption, distribution, hepatic metabolism, and clearance (Table 1) [2, 3]. Pharmacodynamic changes are caused by an abnormal response of the body to drugs. These alterations can be clinically relevant to certain drugs, such as opioids, some benzodiazepines, hypnotics, and anxiolytics, due to the risk of developing or worsening hepatic encephalopathy. Moreover, vasoconstrictor drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), and diuretics may increase the risk of renal dysfunction [4]. Similarly, the risk of renal tubular necrosis associated with aminoglycoside use is increased in patients with decompensated liver cirrhosis and in patients with extrahepatic obstructive jaundice, which is directly related to serum bilirubin levels [5, 6].

NSAIDs should be avoided in cirrhotic patients, especially in those with hydrosaline retention, because they inhibit renal prostaglandin synthesis (essential for the

Table 1 Effects of cirrhosis on the pharmacokinetic and pharmacodynamic properties of drugs

Pharmacokinetic changes		
Absorption	Changes in intestinal permeability and motility	
Hepatic metabolism	↓ Function and expression of enzymes	↑ Oral bioavailability
	↑ Collaterals and portosystemic shunts	↓ First-pass hepatic metabolism ↑ Oral bioavailability
	↓ Glutathione reserves	↑ Toxicity risk
Distribution	↓ Protein synthesis: hypoalbuminemia	↑ Drug-free fraction
	Ascites/edema	↑ Volume of distribution in hydrophilic drugs
Clearance	Biliary excretion	↑ Oral bioavailability
	Renal dysfunction	↑ Oral bioavailability
Pharmacodynamic changes		
↑ Risk of hepatic encephalopathy Renal dysfunction		

maintenance of renal perfusion decreased by the activation of vasoconstrictor systems) and may hasten renal failure [7]. In a prospective cohort study that included 30 patients with NSAID-associated acute kidney injury, 37% developed persistent renal dysfunction, and the remaining 63% developed reversible renal damage. The mortality rate in the group that developed persistent renal dysfunction was 64%, compared to 5% in those with reversible damage [8].

Other drug-related problems in patients with advanced liver disease include lack of adherence, errors due to poor patient understanding, and suboptimal monitoring of treatment and its adverse effects. All these problems lead to increases in adverse events and drug interactions and a higher rate of unscheduled hospital admissions [7, 9].

Unfortunately, there are no tests that accurately determine the degree of impairment of liver metabolic function; therefore, no specific recommendations can be given on the use or dosing of medications in patients with advanced liver disease [7]. Commonly employed liver function grading systems, such as Child–Pugh, do not correlate efficiently with metabolic alterations of the liver. Only general recommendations based on the degrees of first-pass hepatic extraction, hepatic metabolism, and protein binding of each drug can be given. All this information can be obtained from the summary of product characteristics, pharmaceutical databases, or scientific literature. As all of the above may be difficult to perform in patients with advanced liver disease, monitoring the therapeutic effect, watching for the development of adverse effects, and measuring drug levels when possible should be recommended [10].

This article describes prescription data, medication-related problems in patients with advanced liver disease, and how drug-induced liver injury (DILI) can be identified, diagnosed, and managed in these patients.

2 Prescribing Drugs in Advanced Liver Disease

There are few published studies about prescription patterns in patients with advanced liver disease [11]. A prospective multicenter study was conducted in 25 Spanish hospitals and included 568 patients; the prescription of drugs for the treatment of the most frequent complications and comorbidities of cirrhosis was analyzed [12]. One of the observations of the study was a conservative attitude with a tendency to underprescribe drugs. Although the prescription patterns varied greatly from one region to another, the most commonly used drugs were diuretics (59–74%), laxatives (38–76%), vitamin K (0–75%), and beta-adrenergic blocking agents (4–53%) [12].

Another more recent study retrospectively analyzed drug profiles and factors associated with appropriate and inappropriate drug use in more than 12,000 patients with decompensated cirrhosis [13]. An interesting finding of this study was that inappropriate use of drugs was common. More than half of the patients were taking opioids, 46% proton pump inhibitors, 14% benzodiazepines, and 10% NSAIDs. Interestingly, the degree of liver dysfunction was associated with the use of appropriate drugs for complications, but not with the use of harmful drugs for these patients [13].

Due to the prescribing problems reported in patients with advanced liver disease, a structured method based on a literature review and expert opinion was developed to provide recommendations to improve the safety of drug therapy in these patients [14, 15]. Using this method, more than 200 drugs were classified into safe (13.3%), unsafe (13.8%), of unknown effect (17.9%), safe or unsafe

according to the severity of cirrhosis (26.1%), with no additional risks known (27.5%), and with additional risks known (1.4%). This drug classification was used in a retrospective study involving more than 5000 patients with cirrhosis with a mean follow-up of 3 years [16]. The median number of drugs consumed by these patients was nine, and the most prescribed drugs were proton pump inhibitors (53.9%), aldosterone antagonists (43.6%), and sulfonamide diuretics (41.3%). Although 48.3% of prescriptions were drugs with safety recommendations, the prevalence of potentially unsafe drug use was 60% during the total follow-up, with NSAIDs being the potentially unsafe drugs most commonly prescribed [16].

3 Medication-Related Problems in Patients with Advanced Liver Disease

To identify the characteristics and incidence rate of drug-related problems and related preventable harm in critically ill patients with decompensated liver cirrhosis, a prospective observational study was conducted [17]. Medication charts of 78 patients with decompensated cirrhosis admitted to a critical care unit were reviewed by the clinical pharmacist using pharmaceutical tools for the classification of drug-related problems and their outcomes. Almost 400 drug-related problems were identified, most of which were associated with NSAID use, leading to gastrointestinal bleeding (24%) and worsening of renal function (11.5%). Many of these adverse effects could be prevented, with an incidence rate of preventable harm of 78.78 per 1000 patient medical intensive care unit-days. Transient harm occurred in 19.8%, permanent harm in 5.8%, and death in 0.8%. The most frequent drug-related problems identified were drug–drug interactions (49%), guideline nonconformity (16%), inappropriate drug form (12%), and drug contraindication (10%) [17].

In another prospective randomized study, an attempt was made to correct the problems previously detected or to determine how to improve the follow-up of these patients, the pharmacologic prescription, and the control of adverse effects [9]. The study examined medication-related problems in a cohort of 57 ambulatory patients with a history of decompensated cirrhosis who received pharmacist intervention. A total of 375 medication-related problems were identified in these patients, with an average of six per patient. Nonadherence (31.5%) and indication issues (29.1%) were the most prevalent medication-related problems, and the risk of potential harm associated with these problems was low in 18.9% of instances, medium in 33.1%, and high in 48.0%. Moreover, the study showed that the incidence of high-risk medication-related problems was higher the younger the patients, the higher the Child–Pugh score, the greater the Charlson Comorbidity Index, and the more medications patients were taking. As a result of pharmacist intervention, almost 60% of medication-related problems could be resolved, reducing the incidence of unscheduled hospital admissions [9]. These results indicate that there is room for improvement in the prescription and monitoring of patients with advanced liver disease.

4 Hepatotoxicity in Advanced Liver Disease

Hepatotoxicity is of three types. First, direct or intrinsic hepatotoxicity, which is dose dependent, is predictable, has a short latency period, and is reproducible (e.g., acetaminophen DILI). Second, idiosyncratic hepatotoxicity, which accounts for the majority of hepatic adverse reactions, is rare and unpredictable, has a variable latency period, and can result in variable severity. The third type is indirect hepatotoxicity, which is produced by the action of the drug. This in turn can be induced by a new liver disease (e.g., immune-mediated liver disease) or by the reactivation of a pre-existing liver disease (e.g., hepatitis B virus infection in patients receiving immunosuppressive treatment).

According to the International Drug-Induced Liver Disease Consortium (IDILIC), the main biochemical criteria to define acute toxic liver injury are an increase in alanine aminotransferase (ALT) levels $\geq 5 \times$ upper limit of normal (ULN), an increase in alkaline phosphatase levels $\geq 2 \times$ ULN, or the combination of an increase in ALT $\geq 3 \times$ ULN and bilirubin $\geq 2 \times$ ULN. However, patients with underlying liver disease have fluctuations and alterations in their liver profiles for which the standard ULN is not useful. Therefore, in these patients, the ULN should be replaced by their baseline values to detect whether there has been acute liver damage. There are also biochemical criteria for estimating the patterns of liver damage (hepatocellular, cholestatic, or mixed damage). If the ratio between ALT and alkaline phosphatase is ≤ 2, we would be dealing with cholestatic damage; if it is between 2 and 5, it would be mixed damage; and if it is ≥ 5, it would be hepatocellular damage [18–20].

4.1 Diagnosis of Hepatotoxicity

The diagnosis of hepatotoxicity is complex in patients with advanced liver disease, especially because of fluctuations in liver enzyme levels due to the underlying disease [21]. Diagnosis is usually triggered by the detection of alterations in the liver profile over baseline values and subsequent confirmation that these alterations are compatible or not with the patient's underlying liver disease. For example, if a patient with metabolic-associated fatty liver disease develops cholestatic liver damage, this would not fit with the underlying

disease; therefore, another explanation is needed. It is also important to assess the evolution of toxicity after discontinuation of the suspected causative product. There are various methods for assessing causality. One of the most commonly used is the Council for International Organizations for medical sciences/Roussel Uclaf Caussality assessment method (CIOMS/RUCAM) [22]. It is important to bear in mind that the scores obtained on these scales for these patients will be lower than in those with hepatotoxicity without baseline liver disease. Moreover, data on hypersensitivity or unnoticed rechallenge would support the diagnosis of DILI. Sometimes there will be no other choice but to perform a liver biopsy to make a correct diagnosis [21].

An important question is whether patients with chronic liver disease have an increased risk of DILI. This issue has been widely discussed for a long time, and in general, the answer has been negative for most drugs and liver diseases. However, there are exceptions. Administration of antimycobacterial and antiviral drugs to patients with viral hepatitis is known to increase the risk of DILI. In addition, treatment with methimazole, methotrexate, nefazodone, and propoxyphene increases the risk of hepatotoxicity in patients with primary biliary cholangitis, and administration of valproic acid and vitamin A increases the risk of toxicity in patients with alcoholic liver disease [4, 11]. Another question often proposed is whether patients with baseline liver disease have greater severity of DILI. It has long been established that patients with liver disease have higher risks of poor outcome and mortality due to DILI [23, 24].

4.2 Management of Hepatotoxicity

The treatment of hepatotoxicity in patients with advanced liver disease does not differ from those without underlying liver disease. It is based primarily on early diagnosis and discontinuation of the causative agent [25]. However, in some cases, a more specific treatment can be established, such as *N*-acetylcysteine in cases of acetaminophen toxicity, L-carnitine in valproic acid toxicity, cholestyramine in leflunomide toxicity, and the combination of cholestyramine with antihistamines in terbinafine toxicity (Table 2) [25]. The administration of corticosteroids is also accepted in patients with hepatotoxicity with autoimmune features, in situations of hypersensitivity reactions or in the presence of immune-mediated DILI. In patients with severe hepatocellular damage, in addition to supportive measures, orthotopic liver transplantation, dialysis with albumin, or bioartificial systems should also be considered, and in acute hepatic failure due to DILI, *N*-acetylcysteine should be administered until clinical trials corroborate its effectiveness in this scenario [25].

Table 2 Specific treatments for hepatotoxicities caused by some drugs

Liver injury-inducing drug	Treatment suggested
Acetaminophen	*N*-Acetylcysteine
Valproic acid	L-Carnitine
Leflunomide	Cholestyramine
Terbinafine	Cholestyramine + antihistamines

Immune checkpoint inhibitors are increasingly used. Their adverse effects are mainly immune-mediated and have an inflammatory nature, including hepatotoxicity. Risk factors associated with checkpoint inhibitor-induced hepatotoxicity are the type of drug administered, the use of combinations, baseline autoimmune disease, baseline liver disease, and drug dosage [25]. The main features of checkpoint inhibitor-induced liver injury are a latency period of 6–14 weeks and variable symptoms and severity. In the case of anti-CTLA-4, granulomatous hepatitis may develop.

In a study involving 5762 patients treated with immunotherapy, 2% developed hepatotoxicity, which was more frequent when they received combined treatment (9.2%) compared to those receiving monotherapy (1.7%) [26]. As a consequence, 69 patients had to permanently discontinue treatment, and 31 patients discontinued treatment temporarily. In addition, 67 patients received corticosteroids to treat this hepatotoxicity, of whom 14% relapsed after drug de-escalation. The response to corticosteroids and the evolution of the patients were similar between those patients with and without underlying liver disease [26].

Although there have been no clinical trials on the treatment of immunotherapy-induced hepatotoxicity, several algorithms have been proposed according to the initial hepatic profile. Thus, when toxicity is mild (ALT 1–3 × ULN), continuation of checkpoint inhibitors with liver function monitoring is recommended. If toxicity is moderate (ALT 3–5 × ULN or bilirubin 1.5–3 × ULN), it is recommended to temporarily discontinue immunotherapy, rule out other possible causes of the altered liver profile, and administer corticosteroid. If there is no improvement in 7–14 days, mycophenolate mofetil is recommended. Finally, in cases of severe toxicity (ALT > 5 × ULN or bilirubin > 3 × ULN), immunotherapy should be permanently discontinued, ruling out other possible causes of liver disease, and high-dose prednisone should be administered. If there is no improvement in 3–4 days, mycophenolate mofetil should be administered [27].

5 Conclusions

Advanced liver disease presents pharmacodynamic and pharmacokinetic changes that are difficult to measure, as well as an increased risk of drug interactions and adverse effects. Many of the events would be preventable with a good strategy in the control of drug prescription and monitoring of clinical outcomes in these patients. Besides, people suffering from liver disease are at higher risk of developing some forms of hepatotoxicity, which can be more severe and difficult to diagnose. In addition, DILI due to immune checkpoint inhibitors presents different characteristics and management than classic DILI.

To avoid the administration of inappropriate drugs, it is very important to improve the awareness and training of all health care professionals involved in the treatment of patients with advanced liver disease, and also the awareness of patients themselves. Although the hepatic toxicity of some frequently used drugs, such as acetaminophen, is well known, many health care professionals are unaware or not fully aware of the adverse effects that other drugs can have on patients with advanced liver injury, as is the case for NSAIDs.

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