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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Potential drug-drug interactions and adverse drug reactions in patients with liver cirrhosis

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Abstract
Background and aims Patients with liver cirrhosis may be at risk for potential drug-drug interactions (pDDIs) and/or adverse drug reactions (ADRs) due to the severity of their disease and comorbidities associated with polypharmacy.
Methods We performed a cross-sectional retrospective study including 400 cirrhotic patients and assessed diagnoses, medication patterns, pDDIs, and ADRs at hospital admission.
Results The median (range) age of the patients was 60 (21–88) years; 68.5% were male. They had a total of 2,415 diagnoses, resulting in 6 (1–10) diagnoses per patient. Frequent were diagnoses of the digestive system (28.4%), circulatory system (14.2%), blood and blood-forming organs (8.7%), and psychiatric disorders (7.5%); 60.7% of the diagnoses were not liver-associated. The median number of drugs per patient was 5 (0–18), whereof 3 (0–16) were predominantly hepatically eliminated. Drugs were primarily indicated for gastrointestinal, cardiovascular, or nervous system disorders, reflecting the prevalent diagnoses. In 112 (28%) patients, 200 ADRs were detected, mainly associated with spironolactone, torasemide, furosemide, and ibuprofen. In 86 (21.5%) patients, 132 pDDIs were detected. Seven of these pDDIs were the direct cause of 15 ADRs, whereof 3 resulted in hospital admission. Patients with ADRs were older, had more comorbidities, were treated with more drugs, and had a worse renal function and more pDDIs than patients without ADRs.
Conclusions Pharmacotherapy is complex in cirrhotic patients. Hepatologists should know the principles of dose adjustment in cirrhosis and renal failure, but also the most important pDDIs of the drugs used to treat liver disease and comorbidities in this population.

Keywords Liver cirrhosis · Drug-drug interactions · Adverse drug reactions · Dose adjustment

Abbreviations

pDDIs	Potential drug-drug interactions
ADRs	Adverse drug reactions
NSAIDs	Nonsteroidal anti-inflammatory drugs
Q_0	Extrarenal elimination fraction
ATC code	Anatomical Therapeutic Chemical Classification System
ACE	Angiotensin-converting enzyme
HSCT	Hematopoietic stem cell transplantation
RAAS	Renin angiotensin aldosterone system
SSRI	Selective serotonine reuptake inhibitor
COX	Cyclooxygenase

Introduction

Liver cirrhosis remains a frequent cause of morbidity and mortality in most countries, including countries in Europe. Between 1997 and 2001, the yearly mortality rate due to liver cirrhosis was between 9.7 (Netherlands) and 43.5

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(Austria) per 100,000 males and between 5.6 (Sweden) and 16.7 (Austria) per 100,000 females [1].

Since the liver plays a crucial role in the metabolism of endogenous and exogenous substances, impaired hepatic function may influence the pharmacokinetics of drugs used in cirrhotic patients. The absorption process may be altered [2, 3] and bioavailability may be increased due to porto-systemic shunting [2, 4]. The free fraction and possibly also the free concentration of highly protein-bound drugs is increased in patients with hypoalbuminemia [2]. Finally, hepatic drug clearance is usually decreased due to lower hepatic blood flow [2, 5] and decreased activity of phase I enzymes [2, 6, 7]. Pharmacodynamic changes are also prevalent in patients with liver cirrhosis. Increased sensitivity has been shown for central effects of morphine [8] and benzodiazepines [9] and for renal adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs) [10].

All of these factors can potentially influence the effectiveness of a drug and/or the likelihood that a drug is causing adverse reactions. Adverse drug reactions (ADRs) may further increase morbidity and mortality in patients with liver disease.

The current study had several aims concerning drug treatment of patients with liver cirrhosis. First, we wanted to find out which drugs are commonly prescribed in this group of patients. Secondly, we investigated the quantity and severity of potential drug-drug interactions (pDDIs) in these patients. Thirdly, we identified the ADRs. For this purpose, we characterized the medication pattern of 400 patients with liver cirrhosis and assessed the prevalence of pDDIs and ADRs at hospital admission.

Methods

Patients

In the present cross-sectional, retrospective study, we included 400 patients with liver cirrhosis diagnosed by liver histology and/or typical clinical, sonographic, and computer tomographic signs. They were hospitalized at the University Hospital, Basel, Switzerland, between January 2002 and December 2007. The protocol of the study was accepted by the cantonal Ethics Committee.

Data collection

For each patient, demographic and clinical data, diagnoses, drugs administered, characteristics of the drugs administered (dosage and extrarenal elimination fraction, Q_0), and pDDIs and ADRs [11] were collected at hospital admission. Creatinine clearance was calculated by the Cockcroft Gault equation [12]. Severity of liver cirrhosis was classified by the Child Pugh Score [13]. Drugs were grouped according to the Anatomical Therapeutic Chemical Classification System (ATC code). Drugs with a $Q_0 \geq 0.5$ were defined as primarily hepatically eliminated. Potential DDIs were determined by screening the drug profiles using the online version of DRUG-REAX (Micromedex® 1.0 Healthcare Series, http://www.micromedex.com). Only pDDIs with moderate or major severity were considered. All ADRs were classified with a definite, probable, or possible causality rating as described previously [14].

Statistical analysis

The data were descriptively analyzed using Excel and/or SPSS (version 15.0). Comparisons between patients with ADRs and those without ADRs were performed using Student's *t*-test or the chi-squared test without correction for repetitive testing. A significance level of 5% was chosen.

Results

Patient characteristics

All patients studied were adults with males being more prevalent than females (supplementary Table 1). Most patients were in the Child Pugh classes B and C. The most frequent cause of liver cirrhosis was alcohol (69.8%), followed by viral hepatitis (13.5%) or a combination of both (9.7%). Almost 20% of the patients died during hospitalization, reflecting the severity of this disease.

The patients had a total number of 2,415 diagnoses at hospital admission, resulting in a median number of 6 (1–10) diagnoses per patient (supplementary Table 2). Most common were diseases of the digestive (28.4% of all diagnoses) or circulatory system (14.2%) as well as diseases of the blood and blood-forming organs (8.7%) and psychiatric disorders (7.5%). Approximately 40% of all diagnoses were associated with liver cirrhosis, e.g., spontaneous bacterial peritonitis, esophageal varices, and variceal bleeding.

Medication at hospital admission

The patients had a total of 1,999 drugs at hospital admission (Table 1). The median number of drugs per patient was 5 (0–18); a median of 3 (0–16) were predominantly hepatically eliminated. Most prevalent were drugs affecting the alimentary tract and metabolism, mainly vitamins and proton pump inhibitors, as well as drugs for

Table 1 Drugs at hospital admission for patients with liver cirrhosis (n=400 patients)

	Number of drugs (% of patients receiving corresponding drug)	Number of drugs with $Q_0 \geq 0.5$[a] (% of patients receiving corresponding drug)
Number of drugs at hospital admission	1,999	1,360
Drugs per patient at hospital admission[b]	5 (0–18)	3 (0–16)
Alimentary tract and metabolism[c]	650	255
Vitamins[c]	207	6
Thiamine	89 (22.3%)	0
Proton pump inhibitors	154 (38.5%)	154 (38.5%)
Osmotically acting laxatives	83(20.8%)	0
Blood glucose–lowering drugs (excl. insulins)[c]	65	38
Magnesium	33 (8.3%)	0
Insulins and analogues	27 (6.8%)	27 (6.8%)
Calcium	27 (6.8%)	0
Propulsives	12 (3.0%)	12 (3.0%)
Potassium	11 (2.8%)	0
Cardiovascular system[c]	633	532
Potassium-sparing diuretics[d]	160 (40.0%)	160 (40.0%)
Loop diuretics (high ceiling)	157 (39.3%)	127 (31.8%)
Betablockers	146 (36.5%)	134 (33.5%)
Propranolol	78 (19.5%)	78 (19.5%)
ACE inhibitors	34 (8.5%)	8 (2.0%)
Calcium antagonists	25 (6.3%)	25 (6.3%)
Statins	23 (5.8%)	23 (5.8%)
Angiotensin receptor blockers	19 (4.8%)	19 (4.8%)
Thiazides	19 (4.8%)	0
Organic nitrates	12 (3.0%)	12 (3.0%)
Amiodarone	7 (1.8%)	7 (1.8%)
Nervous system[c]	270	257
Benzodiazepines and related drugs	102 (25.5%)	102 (25.5%)
Lorazepam	28 (7.0%)	28 (7.0%)
Zolpidem	27 (6.8%)	27 (6.8%)
Oxazepam	14 (3.5%)	14 (3.5%)
Diazepam	13 (3.3%)	13 (3.3%)
Opioids	58 (14.5%)	58 (14.5%)
Methadone	29 (7.3%)	29 (7.3%)
Antidepressants, excl. SSRI[e]	30 (7.5%)	30 (7.5%)
SSRI	21 (5.3%)	21 (5.3%)
Neuroleptics	17 (4.3%)	15 (3.8%)
Antiepileptics	16 (4.0%)	10 (2.5%)
Dopaminergic agents	8 (2.0%)	8 (2.0%)
Blood and blood-forming organs[c]	154	96
Phytomenadione	44 (11.0%)	44 (11.0%)
Platelet aggregation inhibitors (incl. aspirin low dose)	30 (7.5%)	30 (7.5%)
Iron	26 (6.5%)	0
Oral anticoagulants	21 (5.3%)	21 (5.3%)
Heparins	15 (3.8%)	2 (0.5%)
Folic acid	13 (3.3%)	0
Musculoskeletal system[c]	93	89
NSAIDs	28 (7.0%)	28 (7.0%)
Paracetamol	23 (5.8%)	23 (5.8%)

Table 1 (continued)

	Number of drugs (% of patients receiving corresponding drug)	Number of drugs with $Q_0 \geq 0.5$[a] (% of patients receiving corresponding drug)
Allopurinol[f]	14 (3.5%)	14 (3.5%)
Aspirin, analgesic	8 (2.0%)	8 (2.0%)
COX-2 inhibitors	7 (1.8%)	7 (1.8%)
Respiratory system[c]	75	43
Anti-infectives for systemic use[c]	63	30
Antivirals[c]	38	20
Antibacterials	25 (6.3%)	10 (2.5%)
Fluoroquinolones	9 (2.3%)	4 (1.0%)
Systemic hormonal preparations, excl. sex hormones and insulins[c]	31	31
Corticosteroids	16 (4.0%)	16 (4.0%)
Thyroid hormones	13 (3.3%)	13 (3.3%)
Antineoplastic and immunomodulating agents[c]	15	10
Genito-urinary system and sex hormones[c]	10	9
Various[c]	5	5

[a] Only drugs with known Q_0 included

[b] Data are presented as median (range)

[c] One individual patient may have >1 drug of the corresponding group, % not calculated

[d] Spironolactone accounts for 97.5% of this group. It is mainly converted to active metabolites (the two major ones being canrenone and 7-alpha-thiomethylspironolactone), which are primarily renally eliminated

[e] Including tri-, tetracyclic antidepressants, and venlafaxine

[f] Allopurinol is rapidly converted by the liver to the slightly less active oxypurinol, which is renally eliminated. Dosage adjustment is necessary in both patients with liver and renal insufficiency

the cardiovascular system, primarily potassium-sparing diuretics, loop diuretics, and betablockers. Approximately 10% of all patients were treated with an angiotensin-converting enzyme (ACE) inhibitor. The most frequent drugs for the nervous system were benzodiazepines and benzodiazepine-related drugs as well as opioids. Eleven percent of the patients were treated with phytomenadione, 7.5% with platelet-aggregation inhibitors, and 5% with oral anticoagulants. Astonishingly, 11% of the patients were treated with a COX inhibitor (NSAIDs, analgesic aspirin, or COX-2 inhibitor).

About 68% of all administered drugs were eliminated primarily hepatically ($Q_0 \geq 0.5$).

pDDIs and ADRs at hospital admission

In 21.5% of all patients, a median of 1 (1–5) pDDI was detected (Table 2). Most prevalent possible adverse reactions due to pDDI were hyperkalemia (potassium-sparing diuretics, ACE inhibitors, and potassium chloride), hypoglycemia (betablockers combined with insulin, sulfonylureas, and/or repaglinide), increased bleeding risk (anticoagulants such as dalteparin or phenprocoumon combined with NSAIDs), respiratory depression (benzodiazepines combined with opiates or phenobarbital), and cardiac problems (cardiac depression, QT prolongation). Of all pDDIs, 12.9% resulted in an ADR.

ADRs were detected in 28% of the patients at entry (Table 3). Relative to the number of patients in each Child Pugh class, patients in class Child Pugh A were more frequently affected by ADRs (35.7% of patients) than those in class Child Pugh B (26.1%) or Child Pugh C (26.6%). Nonetheless, most ADRs (43.0%) occurred in patients with liver cirrhosis Child Pugh C. The drugs most frequently associated with an ADR were spironolactone, torasemide, furosemide, and ibuprofen. Most frequently, ADRs resulted in metabolic disorders (mainly hyperkalemia or hyponatremia associated with diuretics and/or ACE inhibitors), in gastrointestinal bleeding (associated with the use of NSAIDs or oral anticoagulants), and in urinary system disorders (mainly worsening renal function due to the use of diuretics and/or ACE inhibitors). Five percent of all ADRs affected the liver and/or the biliary system.

Sixteen ADRs (8%) were the cause of hospital admission. These ADRs consisted of gastrointestinal bleeding associated with low dose aspirin, ibuprofen, or phenprocoumon; hyperkalemia associated with spironolactone or perindopril; and worsening renal function or ascites accumulation associated with ibuprofen. Fifteen ADRs

Table 2 Major and moderate pDDIs in patients with liver cirrhosis (n=400 patients)

DDI/potential outcome	Number of pDDIs	Interacting drugs (number of cases)
Total pDDIs	132 (100%)	
Major pDDIs	56 (42.1%)	
Moderate pDDIs	76 (57.9%)	
Number of different pDDIs	91	
Number of patients with ≥1 pDDI	86 (21.5% of all patients)	
pDDIs per patient[a, b]	1 (1–5)	
DDIs resulting in an ADR	17 (12.9% of all pDDIs)	
Hyperkalemia	24 (18.2%)	Major: Potassium-sparing diuretics + ACE inhibitors (9); potassium chloride + spironolactone (4), potassium chloride + lisinopril (1)
+ risk for nephrotoxicity	9 (6.8%)	Moderate: Spironolactone + valsartan (1)
		Moderate: Potassium-sparing diuretics + NSAID (9)
Hypoglycemia	23 (17.4%)	Moderate: Betablocker + insulin (14), betablocker + sulfonylureas (8), betablocker + repaglinide (1)
Increased bleeding risk	17 (12.9%)	Major: Dalteparin + acetylsalicylic acid (low dose) (1), dalteparin + clopidogrel (1), dalteparin + phenprocoumon (1), dalteparin + ibuprofen (1), acetylsalicylic acid (low dose) + phenprocoumon (2), acetylsalicylic acid (low dose) + venlafaxine (1)
		Moderate: Phenprocoumon + allopurinol (3), phenprocoumon + amiodarone (3), phenprocoumon + diclofenac (1), acetylsalicylic acid (low dose) + verapamil (2), acetylsalicylic acid (low dose) + ibuprofen (1)
Respiratory depression	10 (7.6%)	Major: Benzodiazepines + opiates (7), benzodiazepines + phenobarbital (2), fentanyl + hydrocodone (1)
Cardiac depression	9 (6.8%)	Major: Betablocker + calcium antagonist (4), betablocker + amiodarone (2)
		Moderate: Digoxin + betablocker (3)
QT prolongation	7 (5.3%)	Major: Amitriptyline + sulfamethoxazole, trimethoprim (2), ciprofloxacin + propafenone (1), fluoxetine + haloperidol (1), fluoxetine + methadone (1), risperidone + tramadol (1), trimipramine + venlafaxine (1)
Digoxin toxicity	6 (4.5%)	Major: Digoxin + hydrochlorothiazide (2), digoxin + spironolactone (2), digoxin + amiodarone (1)
		Moderate: Digoxin + furosemide (1)
Altered methadone exposure	6 (4.5%)	Moderate: Methadone + HIV protease inhibitor (4), methadone + efavirenz (2)
Serotonin syndrome	4 (3.0%)	Major: Mirtazapine + fluoxetine (1), mirtazapine + tramadol (1), mirtazapine + venlafaxine (1), tramadol + venlafaxine (1)
Reduced efficacy of levodopa	4 (3.0%)	Moderate: Levodopa + iron (2), levodopa + levomepromazine (1), levodopa + olanzapine (1)
Other	22 (16.7)	

[a] Referring to the patients with one or more pDDI (n=86)

[b] Data are presented as median (range)

(7.5%) resulted from a DDI; among them five patients with bleeding disorders (gastrointestinal bleeding, epistaxis, anemia), four patients with hyperkalemia, three patients with cardiovascular disorders (hypotension, bradycardia, torsade de pointes) as well as one patient each with a psychiatric disorder, somnolence, and collapse. Three DDI-associated ADRs were the reason for hospital admission, namely gastrointestinal bleeding due to the combination of aspirin (100 mg/day) and phenprocoumon, symptomatic bradycardia due to the combination of amiodarone and propranolol, and hyperkalemia due to the combination of spironolactone and perindopril.

The 36 NSAIDs prescribed (NSAIDs and analgesic aspirin) were associated with 24 ADRs in 18 patients (50% of all patients with a NSAID) (Fig. 1). The most prevalent ADRs due to NSAIDs were gastrointestinal bleeding (14/24), bleeding-associated anemia (3/24), exacerbation of ascites (2/24), and thrombocytopenia (2/24). The 53 ACE inhibitor or sartan prescriptions resulted in 20 ADRs in 10 patients (19% of patients treated with an ACE inhibitor or sartan, Fig. 1). Symptoms observed were worsening renal function (6/20), syncope (4/20), hyperkalemia (3/20), hyponatremia (3/20), and hypotension (2/20). In contrast, of 146

Table 3 Prevalence of ADRs with a definite, probable, or possible causality rating in 400 patients with liver cirrhosis

ADR	Number of ADRs (total; according to Child Pugh A, B, C)	Drugs associated with ADRs[a] (cases according to Child Pugh A, B, C)[b]
Total ADR	200 (100.0%)	Spironolactone (9, 11, 30), torasemide (5, 7, 20), furosemide (4, 1, 10), ibuprofen (1, 4, 6)
Child Pugh A	46 (23.0%)	
Child Pugh B	68 (34.0%)	
Child Pugh C	86 (43.0%)	
Number of ADR per patient[c,d]	1 (1–5)	
Child Pugh A	1 (1–5)	
Child Pugh B	1 (1–5)	
Child Pugh C	1.5 (1–5)	
Patients with ≥1 ADR	112 (28% of all patients)	
Child Pugh A	25 (35.7% of Child Pugh A patients)	
Child Pugh B	41 (26.1% of Child Pugh B patients)	
Child Pugh C	46 (26.6% of Child Pugh C patients)	
ADR with definite/probable causality rating	24 (12.0%) (8, 11, 5)	Spironolactone (3, 1, 1), phenprocoumon (0, 4, 0), ibuprofen (0, 1, 3), acetylsalicylic acid low dose (1, 3, 0)
ADRs with possible causality rating	176 (88.0%) (38, 57, 81)	Spironolactone (6, 10, 29), torasemide (3, 7, 19), furosemide (3, 1, 10), propranolol (2, 2, 3)
ADRs as a reason for hospital admission	16 (8.0%) (6, 5, 5)	Spironolactone (3, 0, 1), acetylsalicylic acid low dose (1, 2, 0), ibuprofen (0, 0, 3), torasemide (2, 0, 1), perindopril (2, 0, 0), phenprocoumon (0, 2, 0)
ADRs due to ≥1 DDI	15 (7.5%) (6, 7, 2)	Major: Spironolactone + ACE inhibitors (1, 0, 1), opiates + benzodiazepines (1, 1, 0), acetylsalicylic acid low dose + dalteparin (0, 1, 0), acetylsalicylic acid low dose + phenprocoumon (0, 1, 0), dalteparin + ibuprofen (1, 0, 0), diltiazem + betablockers (2, 0, 0), amiodarone + propranolol (0, 1, 0)
ADR due to DDI causing hospital admission	3 (2.0%) (1, 2, 0)	Acetylsalicylic acid low dose + phenprocoumon (0, 1, 0), perindopril + spironolactone (1, 0, 0), amiodarone + propranolol (0, 1, 0)
ADR according to system organ class		
Metabolic and nutritional disorders	54 (27.0%) (13, 13, 28)	Spironolactone (4, 6, 17), torasemide (1, 2, 6), furosemide (3, 0, 3), hydrochlorothiazide (1, 2, 0), chlortalidone (3, 0, 0), amiloride (0, 3, 0), ramipril (0, 0, 2), enalapril (0, 2, 0)
Gastro-intestinal system disorders	30 (15.0%) (6, 13, 11)	Acetylsalicylic acid low dose (1, 4, 0) and analgesic (1, 1, 1), ibuprofen (0, 2, 3), mefenamic acid (1, 2, 1), iron (0, 2, 1), spironolactone (0, 0, 3), phenprocoumon (0, 2, 0)
Urinary system disorders	25 (12.5%) (3, 9, 13)	Torasemide (2, 3, 8), spironolactone (2, 2, 6), furosemide (0, 1, 4), enalapril (0, 1, 1), lisinopril (1, 0, 1)
Cardiovascular disorders, general	16 (8.0%) (6, 3, 7)	Furosemide (1, 0, 2), amlodipine (2, 0, 1), diltiazem (2, 0, 0), ramipril (0, 1, 1), spironolactone (1, 0, 1), torasemide (0, 0, 2)
Central and peripheral nervous system disorders	15 (7.5%) (1, 6, 8)	Zolpidem (1, 0, 2), oxazepam (0, 1, 1), propranolol (0, 0, 2), ropinirole (0, 2, 0), spironolactone (0, 1, 1), torasemide (0, 1, 1)
Liver and biliary system disorders	10 (5.0%) (1, 3, 6)	Spironolactone (1, 1, 1), enalapril (0, 1, 1)
Psychiatric disorders	10 (5.0%) (4, 4, 2)	Midazolam (1, 0, 1), oxazepam (0, 2, 0), propranolol (1, 1, 0), zolpidem (1, 0, 1)
Platelet, bleeding and clotting disorders	10 (5.0%) (3, 5, 2)	Spironolactone (1, 0, 1), torasemide (1, 0, 1)
Red blood cell disorders	8 (4.0%) (2, 2, 4)	Ibuprofen (0, 1, 2), torasemide (1, 0, 2)
Heart rate and rhythm disorders	4 (2.0%) (1, 2, 1)	-[e]
Other	18 (9.0%) (6, 8, 4)	-[e]

[a] Most frequent drugs associated with ADR mentioned

[b] Sum of cases may exceed the number of ADRs (more than one drug can cause the same ADR)

[c] Referring to the patients with one or more ADRs (n=112)

[d] Data are presented as median (range)

[e] No drug responsible for more than one case

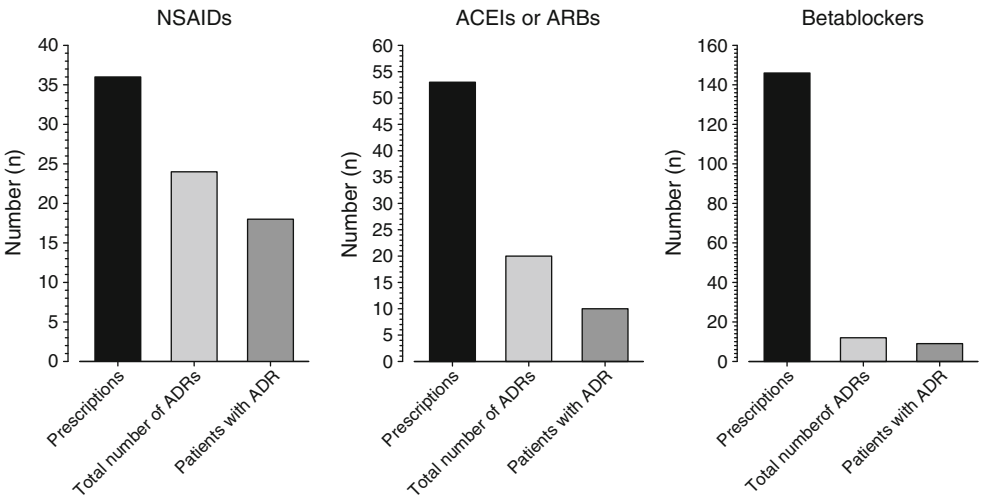

Fig. 1 Number of prescriptions, adverse drug reactions (ADRs), and patients with ADRs for specific drug classes. *NSAIDs* Nonsteroidal anti-inflammatory drugs, *ACEIs* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin receptor blockers

betablocker prescriptions, only 12 ADRs (hypotension, syncope, confusion) were identified in nine patients (6% of all patients with a betablocker, Fig. 1).

Cirrhotic patients with one or more ADR compared with cirrhotic patients without an ADR

When comparing patients with ADRs to those without ADRs (Table 4), patients with ADRs were significantly older than those without ADRs (61 vs. 58 years, $p<0.05$), had a lower creatinine clearance (64.3 vs. 91.6 ml/min, $p<0.001$), had more total diagnoses (6.38 vs. 5.91, $p<0.05$), as well as more non-liver-associated diagnoses (4.20 vs. 3.77, $p<0.05$). They had more drugs prescribed (6 vs. 4, $p<0.001$), as well as more drugs with predominantly hepatic elimination (4 vs. 3, $p<0.001$). Patients with ≥1 hepatically eliminated drug were more prevalent in the ADR group (99.1 vs. 81.6%, $p<0.001$). The same was true

Table 4 Cirrhotic patients with one or more ADRs in comparison with cirrhotic patients without an ADR

Characteristics	Patients with ADR (n=112)	Patients without ADR (n=288)	p-value
Age (years)[a]	61 (35–88)	58 (21–87)	0.017
Male	77 (68.8%)	197 (68.4%)	0.947
Creatinine clearance (ml/min)[a, b]	64 (9–290)	92 (9–280)	0.001
BMI (kg/m^2)[a, c]	24.3 (16.0–42.0)	24.9 (13.5–47.2)	0.997
Child Pugh classification			0.282
Child Pugh A	25 (22.3%)	45 (15.6%)	
Child Pugh B	40 (35.7%)	117 (40.6%)	
Child Pugh C	47 (42.0%)	126 (43.8%)	
Diagnoses per patient[a]	6 (3–10)	6 (1–10)	0.036
Drugs per patient	6 (0–15)	4 (0–18)	<0.001
Drugs with Q_0 ≥0.5 per patient	4 (0–12)	3 (0–16)	<0.001
Patients with ≥1 hepatically eliminated drug	111 (99.1%)	235 (81.6%)	<0.001
Number of pDDIs per patient	0 (0–5)	0 (0–5)	0.012
Patients with ≥1 pDDI	35 (31.3%)	51 (17.8%)	0.004
Length of hospital stay (days)[a]	12 (1–77)	14 (2–116)	0.984
Patients died during hospitalization	23 (20.5%)	44 (15.3%)	0.233
Cause of cirrhosis			0.056
Alcohol	87 (77.7%)	192 (66.7%)	
Viral hepatitis	9 (8.0%)	45 (15.6%)	
Both	7 (6.3%)	32 (11.1%)	

[a] Data are presented as median (range)

[b] Due to incomplete data (body weight, serum creatinine), n=107 and 279 for patients with and without ADR, respectively

[c] Due to incomplete data (body weight, height), n=63 and 186 for patients with and without ADR, respectively

for patients with ≥1 pDDI at hospital admission (31.3 vs. 17.8%). Furthermore, pDDIs were more prevalent in patients with ADRs than in the control group (0.50 vs. 0.26 per patient, $p<0.05$).

Discussion

Studies on patients with liver cirrhosis focusing on drug therapy and drug related problems are scarce in the literature. Lucena et al. investigated prescribing patterns and drug use in patients with liver cirrhosis [15, 16]. To prevent or treat complications of cirrhosis, diuretics, anti-ulcer drugs, laxatives, and vitamin K were the drugs prescribed most often [15]. Frequent medications for nonhepatic comorbidities consisted of insulin, oral antidiabetics, cardiovascular drugs (calcium antagonists, ACE inhibitors, angiotensin receptor blockers), as well as drugs for the nervous (anxiolytics, hypnotics) and respiratory system [16]. The medication pattern of the patients in our study was similar to the patients reported by Lucena et al. [15, 16], suggesting that these studies reliably reflect the medication pattern in cirrhotic patients.

Every fifth patient in our study population had a pDDI, every fourth had an ADR, and 8% of the patients were hospitalized due to an ADR. This is in line with the 5–10% prevalence for ADR-related hospitalizations found in the meta-analysis by Lazarou et al. [17], but slightly more than the 5.1–6.5% reported in a retrospective cohort study [18] and in a prospective observational study [19]. Compared to patients without ADRs, patients with ADRs had more diagnoses and more drugs prescribed, received more drugs eliminated hepatically, had more pDDIs, and had a more compromised renal function.

Polypharmacy is a known risk factor for ADRs [11, 20, 21] and DDIs [22, 23]. Our data indicate that cirrhotic patients who have more comorbidities have more drugs prescribed and are therefore at a higher risk for ADRs. The relationship between number of diagnoses and number of drugs prescribed is well established [23]. The resulting polypharmacy is a risk factor for pDDIs [22, 23] and also for ADRs [11, 20, 21], which may be related to DDIs.

Our data suggest also that treatment with drugs with predominantly hepatic elimination is a risk factor for ADRs. More than 50% of the drugs used in our study fall into this category. Patient exposure to such drugs may be increased mostly due to elevated oral bioavailability and/or decreased hepatic clearance, possibly leading to an increased incidence of dose-dependent ADRs [2]. Astonishingly, systematic publications focusing on hepatically eliminated drugs as a risk factor for ADRs in patients with liver disease are lacking. The drugs with predominantly hepatic elimination associated with ADRs in our population were mostly cardiovascular drugs (torasemide, spironolactone, propranolol, amlodipine, diltiazem), NSAIDs (ibuprofen, acetylsalicylic acid, mefenamic acid), phenprocoumon, and benzodiazepines or related agents (midazolam, oxazepam, zolpidem). If possible, such drugs should be started at a low dose with careful up-titration until reaching a satisfactory drug response or toxicity.

A further risk factor for ADRs is impaired renal function. Impaired glomerular filtration is a well known risk factor for ADRs also in other populations such as the elderly [11, 24]. In our study, patients with ADRs had a lower creatinine clearance as compared to patients without ADRs. Impaired glomerular filtration may be associated with decreased renal clearance and increased exposure to drugs with a predominantly renal excretion. Importantly, patients with liver cirrhosis and ascites can have a creatinine clearance <60 ml/min in spite of a normal serum creatinine [25], mostly due to impaired hepatic formation of creatine and increased tubular secretion of creatinine [2, 26]. Since the Cockcroft formula may overestimate the creatinine clearance in cirrhotic patients, drugs with predominantly renal elimination and dose-dependent ADRs should be dosed very carefully in cirrhotic patients [2].

Another important risk factor for ADRs is the presence of pDDIs. In our study, 7.5% of all ADRs were due to a DDI and 12.9% of the DDIs resulted in an ADR. In a recent review of hospitalized patients on different wards, 17% (range 5–31%) of all ADRs were reported to be due to DDIs [11]. In patients with hematopoietic stem cell transplantation (HSCT), 16% of the ADRs were caused by a DDI and 33% of all DDIs resulted in an ADR [14]. A comparison of the findings in patients with liver cirrhosis suggests that the DDIs in cirrhotics are less severe compared to DDIs in patients with HSCT. This is due to the fact that imidazole and triazole antimycotics used in patients with HSCT are CYP inhibitors interacting with immunosuppressants such as cyclosporin and tacrolimus, which are used routinely in HSCT patients. Nevertheless, pDDIs possibly resulting in severe ADRs are present also in cirrhotic patients; they are known and should be avoided.

The drugs most frequently involved in ADRs and pDDIs in our patients were ACE inhibitors, diuretics, NSAIDs, and oral anticoagulants. ACE inhibitors predispose cirrhotic patients to electrolyte disturbances and renal ADRs. The risk for hyperkalemia in cirrhotic patients treated with ACE inhibitors is increased 5.2-fold compared to patients without liver disease [27]. Patients with liver cirrhosis and portal hypertension have an activation of the renin angiotensin aldosterone system (RAAS) and of the sympathetic nervous system, leading to renal vasoconstriction, impaired renal perfusion and glomerular filtration [28], and increased sodium retention [29]. Since drugs interfering with the RAAS such as ACE inhibitors or sartans can further impair glomerular filtration due to reduced filtration

pressure, they should be used very cautiously in cirrhotic patients. Nevertheless, ACE inhibitors and sartans are prescribed frequently in cirrhotic patients [16].

NSAIDs and COX-2 inhibitors block renal production of prostaglandins, possibly leading to impaired renal perfusion and glomerular filtration, sodium retention, and increase in ascites [2, 10]. Furthermore, NSAIDs may be associated with bleeding from esophageal varices and/or gastrointestinal ulcers due to their toxic effects on gastrointestinal epithelia and inhibition of thrombocyte function. In a case-control study including patients with esophageal varices with or without variceal bleeding, the use of NSAIDs in the week prior to the index day was significantly more common in bleeding patients (OR=2.8) [30]. Taking into account the risks for gastrointestinal bleeding, deterioration of renal function and increase in ascites, it is astonishing that 7% of our patients used NSAIDs and 2% analgesic aspirin. A clearer communication of the risks associated with the use of these drugs and of the analgesic alternatives in this population is therefore necessary.

Our study has several limitations. A first limitation is the retrospective character of the study. The elaborated data were therefore limited to the information provided in the medical records, and it was sometimes not possible to obtain more information on the patient's situation or drug history prior to hospitalization. A second limitation is the limited sample size, which resulted in relatively small numbers of ADRs and DDIs. Nevertheless, we are convinced that the study provides important safety data in patients with liver cirrhosis and helps in identifying medication risks.

From the data of our study, we conclude that patients with liver cirrhosis have many comorbidities predisposing them to polypharmacy, which is associated with pDDIs and ADRs. Besides polypharmacy, important risk factors for ADRs in cirrhotic patients are lack of dose adjustment of drugs eliminated predominantly by the liver or by the kidney and certain pDDIs. Hepatologists should therefore not only know the principles of dose adjustment in patients with liver and/or renal failure, but also the most important DDIs of the drugs used to treat liver disease and comorbidities in this population.

Conflict of interest None of the authors indicates a conflict of interest with this work.

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