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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Dose adjustment in patients with liver cirrhosis: impact on adverse drug reactions and hospitalizations

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Abstract
Aim and background To assess drug-related problems in patients with liver cirrhosis by investigating the prevalence of inadequately dosed drugs and their association with adverse drug reactions (ADRs) and hospitalizations.
Methods This was a cross-sectional retrospective study assessing the dose adequacy of drug treatment of 400 cirrhotic patients at hospital admission based on the authors' own previous studies and standard literature. The prevalence of total and preventable ADRs and of hospitalizations due to preventable ADRs was determined.
Results Of all 1653 drugs prescribed (median 4 per patient), 336 (20 %) drugs were inadequately dosed in 184 patients. Overall, 210 ADRs (78 % preventable) occurred in 120 patients. Sixty-nine ADRs (33 % of all ADRs) were associated with inadequate drug dosing in 46 patients, of which 68 % were preventable. Nonsteroidal anti-inflammatory drugs and psycholeptics in particular frequently caused preventable ADRs associated with inadequate drug dosing. Inadequate drug dosing was more frequently associated with ADRs than adequate drug dosing, and patients receiving inadequately dosed drugs were more frequently admitted to the hospital due to ADRs. Hospitalization of patients receiving inadequately dosed drugs that caused preventable ADRs resulted in 94 additional hospital days.
Conclusion In this retrospective study, inadequate drug dosing was associated with an increased frequency of ADRs, hospital admissions and hospital days in cirrhotic patients. We therefore conclude that the careful dosing of critical drugs is important in patients with liver cirrhosis.

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

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Introduction

The elimination of the majority of drugs on the market depends on liver function. About two-thirds of the drugs on the Swiss market have an extrarenal dose fraction (Q_0) of >0.5 and are thus cleared mainly by the liver. Most patients with liver cirrhosis have an impaired hepatic handling of such drugs, depending on the severity of cirrhosis [1, 2].

In patients with liver cirrhosis, hepatic extraction can be impaired, leading to a substantial increase in the bioavailability of drugs that have a high hepatic extraction in healthy subjects. This is mainly due to an impaired exposure of the hepatocytes to blood because of extra- and intrahepatic shunts [3]. Furthermore, the access of drugs to hepatocytes may be diminished in cirrhotic livers due to capillarization of the sinusoidal endothelium [4].

In addition to this increased bioavailability of drugs, hepatic clearance of most drugs mainly metabolized and/or excreted by the liver is reduced in patients with liver cirrhosis. For drugs with a high hepatic extraction, this is mainly due to impaired blood flow across the liver [1, 2, 5, 6]. For drugs with a low hepatic extraction, metabolism by phase I enzymes, in particular cytochrome P450 enzymes (CYP), is the critical factor [2]. Several investigations have shown that the protein content and/or

the activity of the most important CYPs is reduced in cirrhotic livers [1, 2, 7]. CYPs appear to be more sensitive to liver cirrhosis than phase II enzymes, such as uridine diphosphate glucuronosyltransferase [1].

The free fraction and possibly also the free concentration of highly albumin-bound drugs are increased in patients with hypoalbuminemia, such as those with liver cirrhosis [2]. This may change the kinetic behavior of such drugs, which may be associated with adverse drug reactions. However, not only pharmacokinetic alterations but also pharmacodynamic aspects must also be considered as a potential reason for adverse drug reactions (ADRs) in this patient population. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided by such patients due to the risk for impaired renal perfusion, eventually leading to renal failure [2]. Similarly, susceptibility to central adverse effects of opiates, such as morphine [8], and benzodiazepines [9] is increased in patients with liver cirrhosis.

Due to these pharmacokinetic and pharmacodynamic alterations pharmacotherapy in patients with liver cirrhosis is complex. The high inter-individual variability of these alterations renders pharmacotherapy in cirrhotic patients even more complicated [1, 2].

We recently published a cross-sectional retrospective study presenting demographic data, medication patterns, potential drug–drug interactions and ADRs in 400 patients with liver cirrhosis admitted to the University Hospital of Basel [10]. We found a high prevalence of potential drug–drug interactions and ADRs in this group of patients at hospital admission. In current study presented here, we focused on the quality of dose adjustment in this population and estimated the excess of ADRs and hospitalization days in patients receiving inadequate drug dosing at hospital admission.

Materials and methods

Patients

This work is based on a previously published, descriptive, cross-sectional, retrospective study that investigated diagnoses, medication patterns, potential drug–drug interactions and ADRs in 400 cirrhotic patients at hospital admission[10]. Each patient received a median (range) of five (0–18) drugs, of which three (0–16) were predominantly hepatically eliminated. A total of 200 ADRs with a definite, probable or possible causality-rating were detected in 112 patients (28 %); these ADRs were associated mainly with spironolactone, torasemide, furosemide or ibuprofen. In 86 (21.5 %) patients, 132 potential drug–drug interactions were detected.

Drug categorization

The drugs were classified by their Q_0 and their hepatic extraction (E_h) into five categories. Drugs with a Q_0 of ≥0.5 were considered to undergo mainly hepatic elimination. For drugs with a Q_0 of ≥0.5, the E_h was obtained from the literature (either published as hepatic extraction or calculated from the oral bioavailability and the intestinal absorption, with oral bioavailability defined as the portion of the drug reaching the systemic circulation after oral ingestion; it can be limited by intestinal absorption and by the hepatic first-pass effect). If E_h could not be obtained from the literature, it was estimated using Eq. 1:

$$E_h = \frac{Cl_{sys} \times Q_0}{Q_{plasma}} \quad (1)$$

where Cl_{sys} is the systemic clearance (L/h), Q_0 the extrarenal dose fraction of a specific drug and Q_{plasma} is the hepatic plasma flow (approx. 43 L/h) [11].

The drugs were further categorized according to E_h into the three categories of high hepatic extraction drugs (category 1), intermediate hepatic extraction drugs (category 2) and low hepatic extraction drugs (category 3). Drugs with a Q_0 of <0.5 are excreted mainly by the kidney (category 4). Category 5 refers to drugs with an unknown Q_0 and/or E_h. For further information on this classification, see Fig. 1 and the publications of Delco et al. [2], Tchambaz et al. [12] and Schlatter et al. [13].

Dose assessment and ADRs

Each patient's dose at hospital admission was compared to published dosing recommendations for patients with liver cirrhosis (Fig. 1; [2, 12, 13]) and assessed using a prototypal internal drug database. This database was constructed as described in our previous publications on medication in liver cirrhosis [2, 12, 13]. The recommendations on dosing in patients with liver cirrhosis compiled in this database are based on published kinetic studies for individual drugs and on the recommendations provided in the Physician's Desk Reference (PDR) [14], Micromedex® [15] and/or the Swiss Drug Register [16].

All patients included in the study were on long-term medication and used their maintenance dose at hospital entry; initial doses were therefore not considered in our analysis. According to the general recommendations [2, 12, 13], the maintenance dose for category 1, category 2 or category 3 drugs should be reduced by approximately 50–75, 50 or 0–50 %, respectively, in patients with liver cirrhosis (Fig. 1). Since up-titration according to clinical effect and tolerability is recommended for most drugs, doses that exceeded the general recommendations had to be

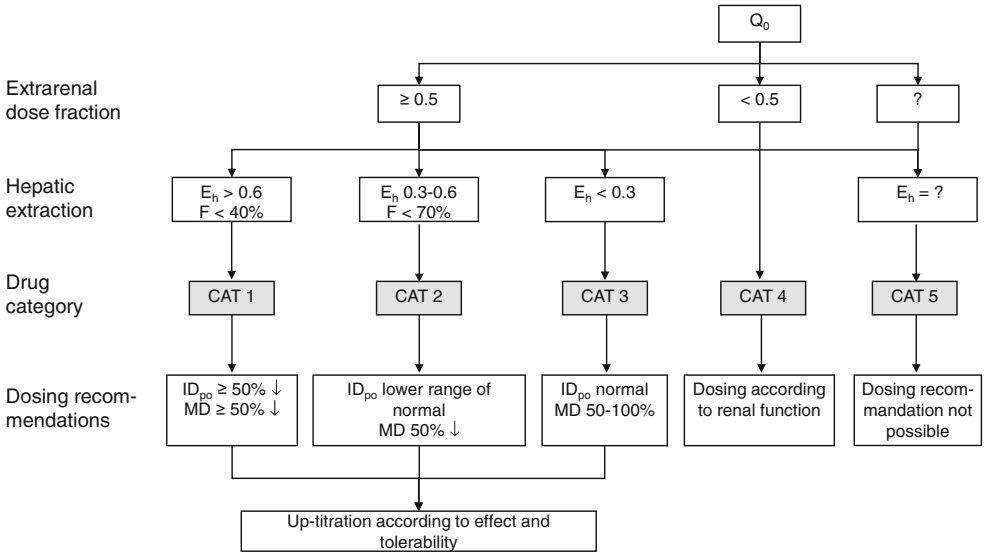

Fig. 1 Classification and dosage recommendations of drugs in patients with liver cirrhosis. Drugs were classified into 5 categories (*CAT*) according to their pharmacokinetic parameters Q_0 (extrarenal dose fraction) and E_h (hepatic extraction). If published data for E_h were not available, E_h was estimated according to Eq. (1) in Materials and methods. If bioavailability after oral administration (*F*) was available, intestinal absorption was also taken into account to estimate E_h. *CAT 1* High hepatic extraction drugs, *CAT 2* intermediate hepatic extraction drugs, *CAT 3* low hepatic extraction drugs, *CAT 4* renal elimination drugs, *CAT 5* drugs with unknown elimination pathway, ID_{po} initial dose administered orally, *MD* maintenance dose

judged individually using the recommendations of the internal database described above. This database provides dosing recommendations adjusted to the severity of liver disease according to the Child class. Accordingly, for each dose assessed, characteristics of the individual patient (in particular the severity of liver disease), as well as of the drug administered (in particular, the existence of dose-dependent, clinically relevant ADRs) were taken into account. For drugs which can be monitored by specific tests (e.g. international normalized ratio for phenprocoumon, blood glucose for insulin and oral diabetics, serum levels), these values were taken into account for judging the dose.

All drugs contraindicated or prescribed in a dose not corresponding to the internal database described above were considered as "inadequately dosed drugs" and were further analyzed. We assessed how many patients received inadequate drug dosing and which category and Anatomical Therapeutic Chemical (ATC) codes were involved.

We identified the ADRs associated with inadequately dosed drugs and classified each ADR as either a type A (dose-dependent, considered to be preventable) or type B ADR (dose-independent, considered not to be preventable). We then assessed the prevalence of total as well as preventable ADRs per drug category. We also investigated the impact of inadequately dosed drugs on mortality. For preventable ADRs associated with inadequate drug dosing as the reason for hospitalization, the excess hospitalization days were determined. Finally, the discontinuation rate of drug treatments at hospital entry was assessed as well as the reasons for discontinuation, in particular inadequate drug dosage and ADRs.

Risk assessment for inadequately administered drugs

To investigate whether inadequate drug dosing was associated with an increased risk for ADRs, we calculated the relative risk for developing ADRs according to the ATC drug category code in patients receiving inadequate drug dosing compared to patients who did not receive inadequate drug dosing and expressed it as an odds ratio (OR). A significance level of 5 % was chosen.

Contraindicated drugs

The Physicians' Desk Reference (PDR) [14] was consulted to check if the prescribed drugs were formally contraindicated in patients with liver disease. Drugs not listed in the PDR were checked in Micromedex® [15], and drugs listed neither in the PDR nor in Micromedex® were judged by means of our internal database which is based on data retrieved from published studies. According to our database, NSAIDs are contraindicated in patients with liver cirrhosis due to an increased risk for ADRs, in particular gastrointestinal bleeding and/or renal failure [2, 17, 18]. This assessment is supported by the results of our previous study, showing a poor tolerability of these drugs by patients with liver cirrhosis [10]. We also investigated the

question of whether ADRs were more frequently associated with contraindicated than with not contraindicated drugs.

Proton pump inhibitors and bacterial infections

Recently published studies suggest that proton pump inhibitors may be associated with an increased risk for spontaneous bacterial peritonitis and/or *Clostridium difficile* infections in patients with liver cirrhosis [19, 20]. Since we did not address the association between proton pump inhibitors and these infections in our previous study, we investigated it in the current one. We considered these ADRs to be dose independent based on our analysis.

Results

Drug categories at hospital admission

At hospital admission, the 400 patients with liver cirrhosis [Child categories: A, 70 (18 %) patients; B, 157 (39 %) patients; C, 173 (43 %) patients] had 1653 prescriptions (median 4 drugs per patient, range 0–15), excluding vitamins and minerals. In terms of drug categories, most abundant drugs were those with a low (29.4 %) or high (27.4 %) hepatic extraction, followed by drugs with intermediate hepatic extraction (19.2 %), and drugs with mainly renal (12.3 %) or unknown elimination (11.7 %) (Fig. 2). Details on those drugs with hepatic elimination, for example, individual drug classes, are presented in our previous publication [10].

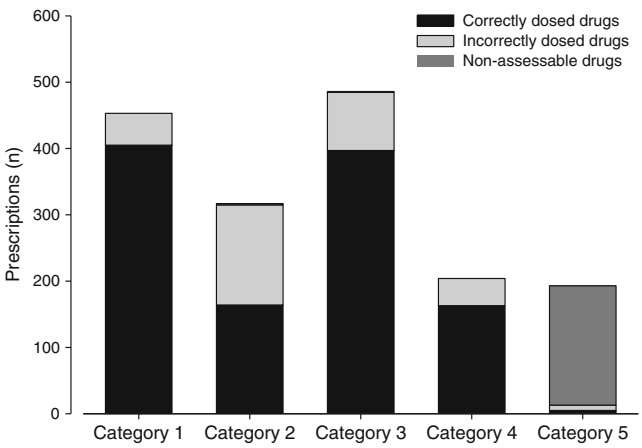

Fig. 2 Fraction of adequately and inadequately dosed drugs according to drug category. *Category 1* Drugs with a high hepatic extraction, *category 2* drugs with an intermediate hepatic extraction, *category 3* drugs with a low hepatic extraction, *category 4* drugs with predominant renal elimination, *category 5* drugs with unknown elimination pathway

Dose assessment and ADRs

Overall, 336 (20.3 %) of all drugs (47.6 % of category 2, 20.1 % of category 4, 18.1 % of category 3, 10.6 % of category 1, 4.1 % of category 5; Fig. 2) were assessed to have been dosed inadequately in 184 patients. Thirty-six of these drugs were contraindicated in patients with liver cirrhosis, and 300 were administered at inappropriately high doses. The majority of drugs (68.4 % of all drugs; 89.4 % of category 1, 81.7 % of category 3, 80.0 % of category 4, 51.7 % of category 2, 2.5 % of category 5) were dosed adequately, and 11.1 % of all drugs could not be assessed regarding dosing (not assessable drugs). According to the ATC code, the drugs most frequently inadequately dosed were those for the alimentary tract and metabolism (ATC A; n=137), nervous system (ATC N; n=80), cardiovascular system (ATC C; n=62) and musculo-skeletal system (ATC M; n=31) (Fig. 3). The ATC drug classes most often involved in ADRs were AO2 (drugs for acid-related disorders), A10B (oral blood glucose-lowering drugs), M01A (non-steroidal anti-inflammatory and antirheumatic products), N05C (hypnotics and sedatives) and N02B (other analgesics and antipyretics).

In total, 210 ADRs (164 preventable reactions, 78.1 % of all ADRs) occurred in 120 patients [median 1 (range 1–5) per affected patient]. Forty-seven ADRs (22 % of all ADRs) occurred in Child A patients, 68 (33 %) in Child B patients and 95 (45 %) in Child C patients. Of all ADRs, 69 [29 % of all ADRs; 47 (68 %) of them preventable) were associated with inadequate drug dosing in 46 patients. Fourteen of

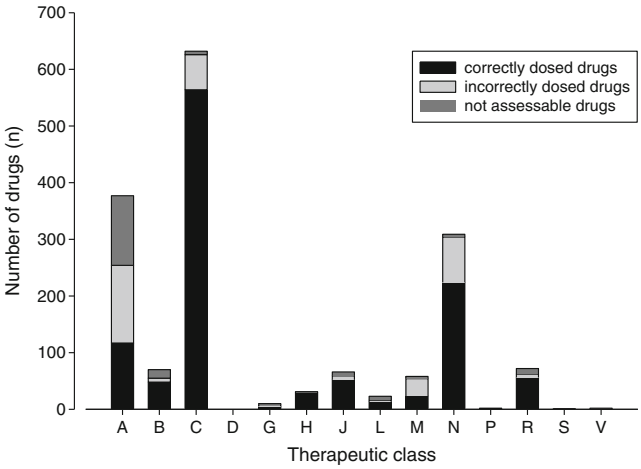

Fig. 3 Fraction of each drug class (ATC code) with adequately and inadequately dosed drugs. *A* Alimentary tract and metabolism, *B* blood and blood forming organs, *C* cardiovascular system, *D* dermatologicals, *G* genito-urinary system and sex hormones, *H* systemic hormonal preparations (excl. sex hormones and insulin), *J* antiinfectives for systemic use, *L* antineoplastic and immunomodulating agents, *M* musculo-skeletal system, *N* nervous system, *P* antiparasitic products, insecticides and repellents, *R* respiratory system, *S* sensory organs, *V* various

these ADRs (20 %) occurred in Child A patients, 21 (31 %) in Child B patients and 34 (49 %) in Child C patients.

ADRs associated with inadequate drug dosing are listed in Table 1. In particular, NSAIDs and psycholeptics and drugs for acid-related disorders were frequently involved in these ADRs. Low, intermediate and high hepatic extraction drugs were associated with 29, 28 and eight ADRs caused by inadequate drug dosing, respectively. Seven of the ADRs were due to a drug–drug interaction.

Twenty-four ADRs in 24 patients were the reason for hospital admission. Of these 24 ADRs, six (25 %), six (25 %) and 12 (50 %) occurred in Child class A, B and C patients, respectively. Noticeably, patients with inadequately dosed drugs (n=20, 10.9 %) were more frequently admitted to the hospital due to an ADR than patients with adequately dosed/not assessable drugs (n=4, 1.9 %). ADRs leading to hospital admission were spontaneous bacterial peritonitis associated with omeprazole, esomeprazole or pantoprazole; *Clostridium difficile* infection associated with omeprazole or esomeprazole; gastrointestinal bleeding associated with diclofenac, ibuprofen, piroxicam or phenprocoumon; coma associated with midazolam; worsening of ascites associated with ibuprofen. Of the 20 ADRs leading to hospital admission associated with inadequate drug dosing, six were considered to be preventable. These six patients stayed in the hospital for a total of 94 days.

As shown in Fig. 4, overall, ADRs occurred more frequently in cases of inadequate drug dosing than in cases of adequately dosed drugs (overall: 20.5 vs. 13.5 % of the prescribed drugs; preventable: 14.0 vs. 10.6 %). Surprisingly, this was not the case for all drug categories. For example, ADRs were less frequent in category 1 drugs that were dosed inadequately compared to those dosed adequately (16.7 vs. 20.0 %, respectively); the same was true for drugs primarily eliminated renally (category 4; 12.2 vs. 25.2 %, respectively). In the other drug categories (categories 2, 3, 5), more ADRs occurred in cases of inadequate drug dosing compared to adequate drug dosing, with the difference being

Table 1 Adverse drug reactions associated with inadequate drug dosing

Drug class (ATC code)	Drugs[a]	Preventable ADRs[a]	Other ADRs[a]
Anti-inflammatory and antirheumatic products (M01)	Ibuprofen (11[b]), diclofenac (7[b]), mefenamic acid (6[b]), piroxicam (1[b])	Gastrointestinal hemorrhage/ulcer (12[b]; 1 DDI), anemia (3[b]), worsening of ascites (2[b]), hyperkalemia (1[b]; 1 DDI), reduction of creatinine clearance (1[b]), psychomotor agitation (1[b]), epistaxis (1[b]; 1 DDI)	Thrombocytopenia (2[b]), leucopenia (1[b])
Psycholeptics (N05)	Zolpidem (6), diazepam (2[b], 1), midazolam (2), pipamperon (1)	Somnolence (3), confusion (1[b], 2), gait disorder (1), mental deceleration (1; 1 DDI), fall (1[b])	Somnambulism (1), elevated ALT (1)
Drugs for acid related disorders (A02)	Omeprazole (3), esomeprazole (3), pantoprazole (2), lansoprazole (1),		Spontaneous bacterial peritonitis 6), *Clostridium difficile* infection (2), elevated ALT (1)
Diuretics (C03)	spironolactone (6), torasemide (2)	Reduction of creatinine clearance (3), hyperkalemia (2; 1 DDI), hyponatremia (1)	Anemia (1), diarrhea (1)
Drugs used in diabetes (A10)	Metformin (3), rosiglitazone (2)	Loss of appetite (1), diarrhea (1), heart failure (1)	Thrombocytopenia (1), hyperbilirubinemia (1)
Calcium channel blockers (C08)	Amlodipine (4)	Edema (2), dyspnea (1)	Hyperbilirubinemia (1)
Agents acting on the renin–angiotensin system (C09)	Ramipril (2), losartan (2)	Syncope (1), hyperkalemia (1), hypotension (1)	Eosinophilia (1)
Antithrombotic agents (B01)	Phenprocoumon (1)	INR increased (1)	
Antineoplastic agents (L01)	Doxorubicin (1)	Neutropenic fever (1; 1 DDI)	
Analgesics (N02)	Acetylsalicylic acid (1[b])	Gastrointestinal ulcer (1[b])	
Other nervous system drugs (N07)	Methadone (1)	Torsade de pointes (1; 1 DDI)	

ATC, Anatomical Therapeutic Chemical classification system; ADR, adverse drug reaction; ALT, alanine aminotransferase; AP, alkaline phosphatase; DDI, drug–drug interaction

[a] Number given in parenthesis is the number of ADRs

[b] Contraindicated drug/ADRs associated with contraindicated drug

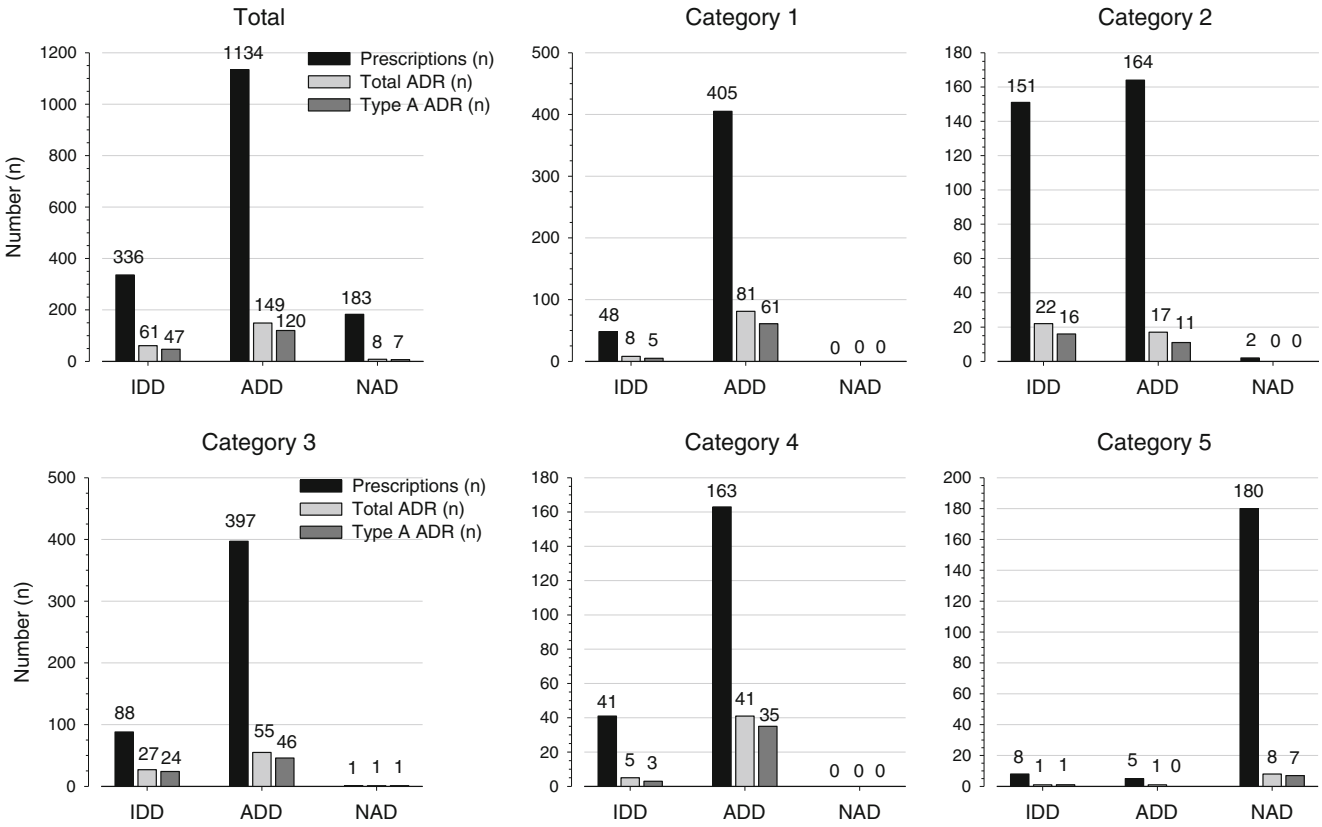

Fig. 4 Number of prescriptions, total number of adverse drug reactions (*ADRs*) and number of preventable (*Type A*) ADRs stratified per drug category. Within each drug category, prescriptions and ADRs are further classified per adequacy of dose adjustment. *ADDs* Adequately dosed drugs, *IDDs* inadequately dosed drugs, *NAD* non-assessable drugs. The sum of the ADRs can exceed the total number of ADRs, since ADRs caused by more than one drug (e.g. one inadequately as well as one adequately dosed drug) were counted more than once

most pronounced in category 3 drugs (33.0 vs. 14.1 %, respectively) followed by category 2 drugs (18.5 vs. 12.2 %, respectively). For category 5, we compared the drugs which are contraindicated or not recommended in liver cirrhosis with the other drugs in this group (adequately dosed drugs and not assessable drugs) and found that ADRs occurred more frequently with drugs that are contraindicated/not recommended in liver cirrhosis (12.5 vs. 4.9 %).

The only ATC group associated with a statistically significant increased risk for ADRs in the case of inadequate drug dosing was the musculo-skeletal system group [ATC M: OR 11.1, 95 % confidence interval (CI) 2.5–66.5; Fig. 5], which contains the NSAIDs.

At hospital admission, the likelihood that treatment with inadequately dosed drugs associated with an ADR would be stopped [total 37/50 (74.0 %); category 4 and 5, 100 %; category 3, 76.2 %; category 2, 70 %; category 1, 60.0 %) did not differ from that with adequately dosed drugs associated with an ADR [total 98/131 (74.8 %); category 5, 100 %; category 4, 88.5 %; category 1, 77.6 %; category 2, 76.5 %; category 3, 60.5 %). Treatment with inadequately dosed drugs not associated with ADRs was less often stopped at hospital admission [total 89/286 (31.1 %); category 5, 57.1 %; category 2, 35.1 %; category 4, 28.9 %; category 3, 26.9 %; category 1, 23.3 %).

An increased mortality rate was observed in patients with ADRs (see below). Adequate dosing, however, had only a minor influence on mortality. In patients with ADRs, mortality was similar in patients with inadequately dosed drugs and those with adequately dosed/not assessable drugs (24.5 versus 23.9 %, respectively). In comparison, in patients without ADRs, mortality rates were 14.6 % in patients receiving inadequate drug dosing and inadequate dose dosing/not assessable drugs.

Contraindicated drugs

Of all drugs, 36 (2.2 %) were contraindicated in patients with liver disease [ibuprofen (12), diclofenac (9), mefenamic acid (5), diazepam (3), atorvastatin (2), acemetacin (1), piroxicam (1), analgesic acetylsalicylic acid (1), methyldopa (1), pravastatin (1)]. The drug categories involved were category 1 drugs with high hepatic extraction (e.g. acetylsalicylic acid, atorvastatin, pravastatin), category 2 with intermediate hepatic extraction (e.g.

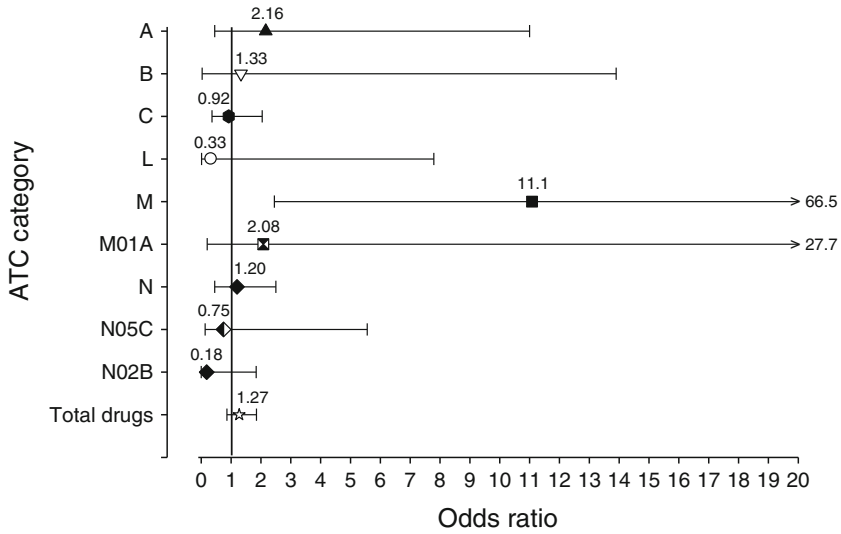

Fig. 5 Odds ratios (95 % confidence intervals) for the risk of developing ADRs according to the quality of dose adjustment. The relative risk for developing ADRs for inadequately versus adequately dosed drugs was calculated for all drugs and different drug classes (ATC code). Odds ratios for unlisted ATC codes could not be calculated. For definition of ATC classes A–C, L–N, see Fig. 3 caption. *M01A* Anti-inflammatory and antirheumatic products (including NSAIDs), *N05C* hypnotics and sedatives, *N02B* other analgesics and antipyretics

diclofenac) and category 3 with low hepatic extraction (e.g. acemetacin, ibuprofen, piroxicam, diazepam, zopiclone, methyldopa), as well as category 5 drugs with unknown elimination (e.g. mefenamic acid).

In total, these drugs caused 28 ADRs (indicated with a superscript 'b' in Table 1). The most frequent ADRs were gastrointestinal hemorrhage/ulcer associated with NSAIDs. Related to prescriptions, approximately sevenfold more ADRs (7.7-fold more preventable ADRs) occurred due to treatment with contraindicated drugs as compared to non-contraindicated drugs.

Proton pump inhibitors and bacterial infections

Eighteen spontaneous bacterial peritonitis and six *Clostridium difficile* infections occurred in the study population, of which nine and three, respectively, were associated with proton pump inhibitors. Patients ingesting proton pump inhibitors suffered more frequently from spontaneous bacterial peritonitis or *Clostridium difficile* infection than patients not taking proton pump inhibitors (7.8 vs. 4.9 %, respectively). Additionally, inadequately dosed proton pump inhibitors were more frequently associated with such infections than adequately dosed proton pump inhibitors (8.9 vs. 6.3 %, respectively). Six hospitalizations were due to spontaneous bacterial peritonitis or *Clostridium difficile* infection associated with inadequately dosed proton pump inhibitors.

Discussion

Drug dosing in 400 cirrhotic patients at hospital entry was assessed using our own recommendations [2, 12, 13], the recommendations provided by Micromedex® [15] and the respective product information [14]. Approximately three-quarters of all drugs (excluding vitamins and minerals) used in this patient population have a predominantly non-renal elimination, in most cases involving the liver. Approximately 20 % of the prescriptions were considered to be inappropriate due to an excessively high dose or a contraindication. Inadequate drug dosing was more frequently associated with ADRs (20.5 % of prescriptions) compared to adequate drug dosing (13.5 % of prescriptions). Patients with inadequately dosed drugs were more frequently admitted to hospital due to an ADR (10.3 vs. 1.9 %) than patients with adequately dosed drugs/not assessable drugs. Since most of the inadequately dosed drugs associated with ADRs were recognized at hospital entry and the appropriate adjustments in therapy taken, the duration of hospitalization and mortality rates were not different between patients with or without inadequately dosed drug(s).

To the best of our knowledge, this is the first published study in which the potential effect of dose adjustment on drug-related problems in patients with liver cirrhosis is reported. A major problem may be that, in contrast to impaired renal function, no generally accepted dose recommendations exist for patients with impaired liver function. This is particularly true for older drugs where recommendations in the product information are often lacking or not helpful (e.g. “drug should be used with caution”) and the problem is shifted to the prescriber.

In comparison to our previous study involving the same group of patients [10], the number of prescriptions in the present study is lower due to the exclusion of vitamins and minerals. Since precise pharmacokinetic data for vitamins and minerals are usually not available, most of these substances would belong to category 5 with an unknown elimination pathway, resulting in an overestimation of this drug category (in our previous study, 17 % of all prescriptions were vitamins and minerals [10]). Taking into account the generally good tolerability of vitamins and minerals, we feel

that their exclusion from our analysis is acceptable. The number of ADRs is higher in the present study than in our earlier study [10]. This is due to the inclusion of spontaneous bacterial peritonitis and *Clostridium difficile* infections, which were considered to be associated with proton pump inhibitors [19, 20].

In our study, 20.3 % of all prescriptions were dosed inadequately in relation to liver function, and inadequately dosed drugs were more frequently associated with ADRs than adequately dosed drugs. This result was expected given that most ADRs are dose dependent. Surprisingly, the number of ADRs associated with inadequate drug dosing was not higher for drugs with a high hepatic extraction (category 1) or predominantly renal elimination (category 4) than for adequately dosed drugs. It appears, therefore, that physicians are aware of the high-risk drugs in these patients and of the necessity for dose adjustment in patients with liver cirrhosis. A contributing factor may be that the maintenance dose of such drugs can be adjusted according to clinical effect and tolerability in each individual patient. For certain drugs, the actual maintenance dose may therefore be higher than that suggested by the recommendations. This is, for example, the case for beta-blockers, which were the most frequent category 1 drugs in our population (e.g. propranolol). Therefore, the dosage of category 1 beta-blockers was assessed only rarely as inappropriate (only in 3 of 109 category 1 beta-blocker prescriptions).

The inadequate dosing of category 4 drugs was mainly due to the prescription of metformin and the dosage of ramipril. Metformin should be avoided in patients with liver cirrhosis due to an increased risk for lactic acidosis, and ramipril should be used only at a low dose, since hemodynamic changes in patients with liver cirrhosis predispose them for renal hypoperfusion and/or hypofiltration, possibly leading to renal failure [2].

In our study, 78 % of all ADRs and 68 % of ADRs associated with inadequate drug dosing were classified as potentially preventable. These numbers correspond well with the frequencies reported in a review published in 2007 [21], stating that 80 % (51–100 %) of adverse drug events in hospitalized patients are potentially preventable. The prevention of such events could be achieved by using the lowest effective dose and by the elimination of drug–drug interactions and other medication errors [21].

NSAIDs were by far the most often prescribed contraindicated drugs in this population: of the 36 contraindicated drugs, 28 were NSAIDs. NSAIDs caused a total 25 ADRs, of which 21 were considered to be preventable and five were a reason for patient hospitalization. Cirrhotic patients treated with a NSAID had a 50 % probability to develop a severe ADR. In total, patients treated with a contraindicated drug (including NSAIDs) had a sevenfold higher risk to suffer from an ADR than patients without contraindicated drugs. These figures highlight the importance that this patient group avoids the use contraindicated drugs, NSAIDs in particular. Interestingly, the use of NSAIDs in cirrhotic patients is not contraindicated in the PDR or Micromedex®, but it is by the Swiss Drug Register. Taking into account the high frequency of the mostly severe ADRs caused by NSAIDs (leading to hospitalization and, potentially, death), NSAIDs should be considered to be contraindicated in cirrhotic patients.

Interestingly, ADRs associated with inadequate drug dosing were most frequently related to drugs causing pharmacodynamic alterations in patients with liver cirrhosis; the drug classes most often involved were NSAIDs, sedatives/hypnotics and oral antidiabetics. While central nervous system-depressing drugs bear an increased risk for hepatic encephalopathy [2], oral antidiabetics may induce hypoglycemia due to impaired drug metabolism and possibly also impaired gluconeogenesis in patients with decompensated liver cirrhosis [22].

Consistent with growing evidence from the literature [19, 20], patients with proton pump inhibitors suffered more frequently from spontaneous bacterial peritonitis or *Clostridium difficile* infection in our study. Proton pump inhibitors reduce gastric acid production, possibly resulting in an impaired gastric barrier against enteric pathogens [19]. An association of acidic suppression with increased bacterial colonization and risk of infection has been observed [19, 23]. Physicians should be aware of these possible ADRs and should very carefully reflect on the indication for proton pump inhibitors in patients with liver cirrhosis.

Our study has several limitations. The retrospective character only allowed us to include the data documented in the medical records, which was not always complete. Furthermore, retrospective studies can generate hypotheses, but this design is not suitable to draw firm conclusions. It has to be realized, however, that not all aspects of the current study could be investigated prospectively; for example, it would be unethical to treat patients with contraindicated drugs.

In conclusion, the results of our study show that approximately 20 % of the prescriptions in patients with liver cirrhosis are inappropriate because of dosage and/or contraindication. Based on these results, we suggest that patients with inappropriate prescriptions, especially those treated with contraindicated drugs, are at a high risk for ADRs, leading to a higher hospitalization rate—and the associated higher costs—due to these ADRs. Careful dosing, especially of drugs used for other indications than liver disease, and the avoidance of contraindicated drugs are therefore mandatory in this group of patients.

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