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Original Communication

Drug choice and dose adjustments in patients with decompensated liver cirrhosis: a retrospective cohort study

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ABSTRACT

Patients with liver disease often require drug therapy. Drug pharmacokinetics and pharmacodynamics can vary dramatically in these patients and careful consideration is needed in drug choice and dosage to avoid adverse effects. In this study, the choice of drugs and their dosage were evaluated in a population of patients with severe liver disease. A retrospective study, using routinely collected hospital and pharmacy data, was conducted among adult patients diagnosed with decompensated liver cirrhosis. Drug choice and dosage were evaluated when patients were admitted to the hospital (at least 3 months after diagnosis). Recommendations in the summary of product characteristics (SPC), reference-books and medical literature were used for comparison. Medication errors were divided into the following categories: 'contra-indicated drug', 'wrong dose', 'required monitoring not executed', and 'wrongly discontinued'. Forty-one patients were included in this study. Their mean age was 59 years and 78% of patients had a history of alcohol abuse. One-third of patients had decompensated liver cirrhosis at the defined evaluation moment. Seventy-three medication errors were identified in 355 prescriptions (22%). Most medication errors were of the categories 'contra-indicated drugs' and 'wrong dose'. Contra-indicated drugs mainly consisted of oral antidiabetics (35%), benzodiazepines (17%), statines (13%) and slow release iron formulations (13%). Wrongly dosed drugs were proton pump inhibitors (65%), paracetamol (15%) and tramadol (8%), mainly prescribed by protocol. Although recommendations on drug choice and dose in patients with severe hepatic dysfunction were present, 1 out of 5 medication orders were incorrect. Most medication errors were made when drugs were prescribed by protocol. Severe hepatic dysfunction was barely taken into account in these cases. Recommendations on drug choice and dose are available to a large extent and, if not, can be easily deducted with basic knowledge of human pharmacology. This population of patients seems particularly suited for the application of personalized medicine.

KEYWORDS: drug choice, dose adjustments, decompensated liver cirrhosis, hepatic dysfunction

INTRODUCTION

The liver is a large organ which plays a major role in the biotransformation of many drugs. Imaginably liver disease can have a large impact on the kinetics and dynamics of drugs [1-5]. Fortunately, the liver has a metabolic overcapacity. Therefore problems are only to be expected in severe cases [6]. A severe complication in advanced liver disease is cirrhosis. Liver cirrhosis is characterized by fibrosis and changes in hepatic vasculature [4, 7]. Important alterations in liver cirrhosis are a decrease in the number and activity of hepatocytes, an increased intrahepatic resistance, shunting, a decrease in liver protein synthesis and changes in biliary secretion [1, 4]. The effects of these alterations are unpredictable and make the choice and dosage of

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drugs extremely difficult [1, 3, 6]. Unlike general belief, a wide variety of recommendations are available for the choice and dosage of drugs in the treatment of liver cirrhosis. Unfortunately these recommendations are not bundled in a ready to use format for prescribers. A recent development is dose adjustments based on Child-Pugh scores [5, 8]. The Child-Pugh score evaluates liver function using five markers: serum bilirubin, serum albumin, international standardized ration (INR) or prothrombin time (PT), the presence of encephalopathy, and the presence of ascites [8]. Based on the obtained score, disease can be classified as class A (5 or 6 points), B (7-9 points) or C (10-15) points.

Drug recommendations can also be based on available literature. An example of a valuable source of recommendations is the 'Guide to drug dosage in Hepatic disease' published by Hebert [9]. Drug recommendations in liver cirrhosis can also be based on general pharmacokinetic considerations. Examples of pharmacokinetic considerations in liver cirrhosis are: avoidance of pro-drugs, avoidance of hepatic cleared drugs, application of phase 2 (conjugation) above phase 1 (oxidation) metabolised drugs, avoidance of drugs with a narrow therapeutic index and reduction of initial and maintenance dose in drugs with high hepatic extraction ratio [1-9].

It is conceivable that prescribers would take appropriate action regarding the choice and dosage of drugs in patients with liver cirrhosis because the information to do so is available. However, to our knowledge there are no data available in the Netherlands regarding drug choice and dosage in patients with liver cirrhosis. The aim of our study is to investigate if physicians consider decompensated liver cirrhosis when prescribing and dosing drugs.

MATERIALS AND METHODS

Patient selection

Patients were selected by running a query in the electronic hospital information system (Chipsoft-EHIS®, Amsterdam, The Netherlands) for patients with the diagnosis-treatment combination (DBC) code for decompensated liver cirrhosis (709), treated by a gastroenterologist/hepatologist from January 1st 2005 to December 31st 2008. Diagnosis and date of diagnosis were confirmed from the medical records of the selected patients.

Study design

The study design was a retrospective cohort study. To give all prescribers a fair chance of being aware that the patients were diagnosed with decompensated liver cirrhosis, the drug evaluation moment was defined as the first day of the first hospital admission at least 3 months after diagnosis.

Clinical medication data were obtained from the electronic hospital information system. Outpatient prescription histories 1 year prior to the drug evaluation moment were collected from the patients' retail pharmacists. Liver function at the drug evaluation moment was determined using the Child-Pugh score. This score uses 5 parameters: serum bilirubin, serum albumin, INR or PT, the presence of encephalopathy and the presence of ascites [8]. Based on the obtained score, disease can be classified as class A (5-6 points/mild disease), B (7-9 points/moderate disease) or C (10-15/severe disease). Laboratory parameters for the calculation of the Child-Pugh score were collected at the drug evaluation moment +/- two weeks.

Drug choice and dosage were evaluated at the drug evaluation moment. Dosing information and contra-indications were primarily obtained from the summaries of product characteristics (SPC's) and two large drug databases: KNMP Kennisbank and Micromedex. Secondly, when recommendations were lacking in these data sources, dosing information and contra-indications were extracted from biomedical literature in PubMed. Finally, if biomedical literature was also absent, drug choice and dosage were evaluated by taking into account basic pharmacological principles (both pharmacokinetics and –dynamics). Concerning the latter, the Food and Drug Administration (FDA) definition of substantial hepatic metabolism and/or excretion was used to judge the importance of hepatic clearance in the total metabolism of a specific drug; substantial in this regard is defined as more than 20% of the parent drug or its active metabolite(s) being eliminated by the liver. A Microsoft Access database was used for the collection and interpretation of patient and medication data.

Ethical considerations

Because this was a retrospective cohort study, the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of Máxima Medical Center concluded that this study did not have to be reviewed by a medical ethics board according to Dutch Law on Medical Research with Humans (WMO). The protocol was in accordance with the Helsinki Declaration and Good Clinical Practice (GCP).

Outcome measures

The primary outcome measures of this study were both the percentage of medication errors in total and those specified for the categories: 'contra-indicated', 'incorrectly dosed' (both dose and frequency), 'no pharmacovigilance' and 'wrongly discontinued'.

Statistical analysis

Descriptive statistics was used to summarize the collected data. Data are expressed as means with range or 95% confidence interval (CI95%).

RESULTS

Patients

Forty-one patients were included in this study. Patient characteristics are shown in Table 1. History of alcohol abuse was present in 86% of men and 70% of women. Other causes of liver cirrhosis were primary biliary cirrhosis, hepatitis B or unknown.

Primary outcomes

Most important findings regarding drug evaluation are shown in Table 2. Seventy-three medication errors were identified among 355 prescriptions (22%). The share of the specific drug classes that were considered contra-indicated is displayed in Figure 1. Oral antidiabetics (n=8) were considered contra-indicated because of an unpredictable effect of sulfonylurea derivatives on glucose homeostasis and relatively high risk of lactate acidosis from metformin in patients with severe liver cirrhosis. Benzodiazepines (n=4), which are metabolized by oxidative metabolism in the liver were considered contra-indicated because of high risk of accumulation [5]. Lorazepam, oxazepam and temazepam, which are metabolized by glucuronidation were therefore considered first choice benzodiazepines in cirrhotic patients. Statines (n=3) lead to an increased risk of hepatotoxicity due to an impaired first-pass metabolism in decompensated liver cirrhosis. Furthermore, the therapeutic surplus value of statines in patients with liver disease is at least questionable because of poor prognosis [10]. Slow release iron formulations (n=3) were considered contra-indicated due to unfavourable release kinetics and the high risk of lesions in the alimentary tract in cirrhotic patients, which often have oesophagus varices.

The share of the specific drug classes that were considered incorrectly dosed are displayed in Figure 2. For proton pump inhibitors (PPI's) (n=31), esomeprazole and pantoprazole at a dose of more than 20 mg daily was deemed incorrectly dosed. Also, exceeding the paracetamol dosing upper limit of 3 g daily (n=7) and a dosing frequency of less than 12 hours for tramadol (n=4) were considered incorrectly dosed [11].

Pharmacovigilance was absent but considered necessary in cirrhotic patients on phenytoin (n=1)

Table 1. Patient characteristics.

	n	%
Total	41	100
Sex (male/female)	21/20	51/49
Age, mean + range (in years)	59	37-79
History of alcohol abuse	32	78
Decompensated liver cirrhosis at evaluation moment	14	34

Table 2. Drug evaluation.

	n	%
Total number of drugs	355	100
different drugs	81	
Total number of medication errors	79	22.3
contra-indicated drugs	23	6.5
wrong dose	48	13.5
required monitoring not executed	3	0.9
wrongly discontinued	5	1.4
Total number correct	261	73.5
no dose adjustment needed	229	64.5
correctly dosed or continued	32	9.0
Unknown	15	4.2

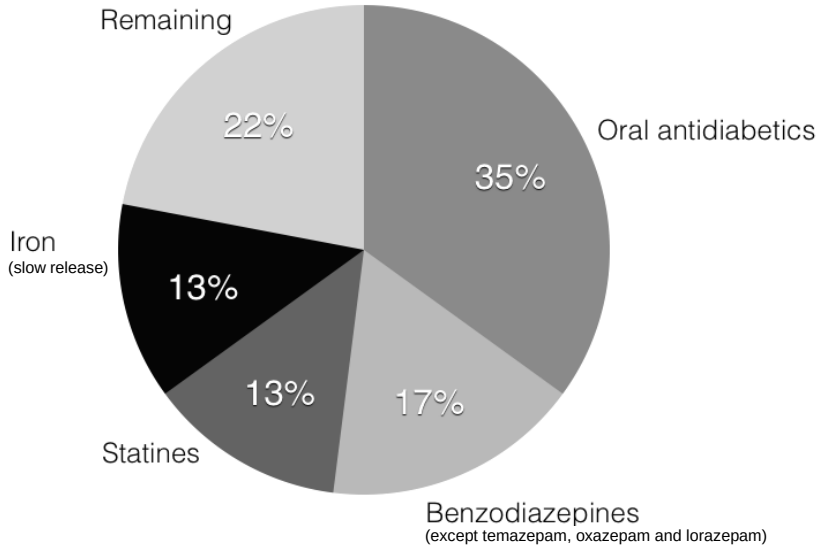

Figure 1. Contra-indicated drugs.

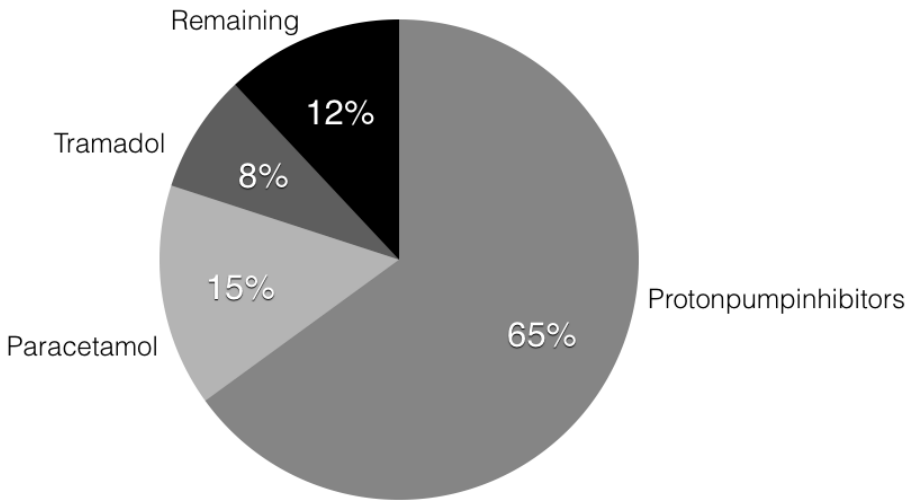

Figure 2. Incorrectly dosed drugs.

or dalteparin (n=2). For phenytoin, therapeutic drug monitoring (TDM) of (the albumin unbound fraction of) serum level is recommended due to the narrow therapeutic window and generally low albumin levels in patients with liver cirrhosis. Before cirrhotic patients are treated with low molecular weight heparins (LMWH's), INR or PT testing is mandatory because of unpredictable coagulation due to reduced production of coagulation factors.

Discontinuing diuretics (n=3) or vitamin B supplements (n=2) was considered malpractice in alcoholics [7]. No conclusions could be drawn if data concerning drug dose were incomplete (n=15), mostly lacking perfusor pump rates or 'by prescription' dosing.

DISCUSSION

Although recommendations for the choice and dosage of drugs in liver impaired patients are available, a (serious) medication error is made in 1 out of 5 patients. Obviously, this is a matter of concern and there is room for improvement.

Patients with liver cirrhosis are par excellence suitable for application of personalized medicine. Drug choice and dosage cannot be considered incorrect in general; this has to be assessed individually instead. Therefore, applying an oral antidiabetic or statin in a patient with long-term decompensated liver cirrhosis is not undesirable per se and can be a rational choice in individual cases [10]. On the other hand, a drug that is normally considered safe in liver cirrhosis can be contra-indicated in individual cases. For instance, in patients with hyperammonemia, all benzodiazepines, even lorazepam, oxazepam and temazepam, are contra-indicated due to the elevated risk on encephalopathy [6].

In this study, the greater part of medication errors was identified for drugs which were prescribed by protocol, such as PPI's, LMWH's and paracetamol. Typically, PPI's are considered safe, but they are associated with spontaneous bacterial peritonitis in cirrhotic patients [12]. For this reason, PPI's should be prescribed with caution and the dosing advice for patients with liver impairment should be followed closely. Likewise, the use of paracetamol, the drug of first choice in many pain protocols, should be restricted in cirrhotic patients. Alcohol abuse is the most occurring cause of liver cirrhosis in the western world, as is also the case in our study population. This leads to cytochrome P-450 2E1 induction and glutathione depletion, both risk factors for developing paracetamol-induced hepatotoxicity [11]. Treatment protocols should not be applied blindly on groups of patients that are at risk in general and on patients with severe liver impairment in particular.

For accurate assessment of the consequences of liver cirrhosis on the effects and adverse reaction of drugs, knowledge of drug pharmacokinetics and pharmacodynamics is mandatory. Although hospital pharmacists pre-eminently possess this knowledge of drug pharmacology, for the present they are consulted minimally regarding this subject. As per so-called 'clinical rules' the hospital pharmacist can identify these patient groups at risk, followed by an individual medication review and tailored advice to the physician. Recommendations on drug choice and dose are present to a large extent and, if not, can be easily deducted with basic knowledge of human pharmacology. When initiating pharmacotherapy in cirrhotic patients, it is important to start low and go slow, titrating the drug to the desired effect. These patients are to be followed meticulously, constantly tailoring pharmacotherapy to actual liver function.

CONCLUSION

Finally, it can be concluded that at present patients with severe liver impairment are underexposed to the personalized considerations of drug choice and dosage. This population of patients seems particularly suited for the application of personalized medicine.

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CONFLICT OF INTEREST STATEMENT

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria, educational grants, participation in speakers' bureaus, membership, employment, consultancies, stock ownership, or other equity interest, and expert testimony or patent-licensing arrangements), or non-financial interests (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

ABBREVIATIONS

CI95%, 95% confidence interval; DBC, diagnosis-treatment combination; FDA, Food and Drug Agency; INR, international standardized ratio; IRB/IEC, Institutional Review Board/Independent Ethics Committee; LMWH, low molecular weight heparine; PPI, proton pump inhibitor; PT, prothrombin time; SPC, summary of product characteristics; TDM, therapeutic drug monitoring

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