Abstract  

Objective: To describe the prescribing patterns for liver disease management.

Methods: A multicenter cross-sectional prospective observational study was carried out in 25 Spanish hospitals. Inpatients, admitted to gastrointestinal and liver units with a diagnosis of liver cirrhosis, were included in five centrally assigned index days between February and June 1999. Information was collected about demographic variables and pharmacological treatments used on admission and recommended at discharge.

Results: Five hundred and sixty-eight patients (70% men, mean age 61 years) were studied. Alcoholic cirrhosis of the liver accounted for 44% of the sample, ascites being the most prevalent complication. The most frequent diuretic schedule on admission was the combination of spironolactone and furosemide at a ratio of 1 (100 mg/40 mg). Hospitalization resulted in an increase in the percentage of patients that received the combination at a ratio higher than 1. Diuretics were a major cause of adverse drug events on admission (7.5%). Ulcer-healing drugs showed a notable increase at discharge (35%; range 10–59%) compared with 24% (6–37%) on admission. Utilization rates at discharge were 65% (59–74%) for diuretics, 51% (38–76%) for laxatives, 31% (0–75%) for vitamin K, 24% (4–53%) for β-adrenergic blocking agents, and 13% (0–47%) for nitrates, which were significantly higher than on admission.

Conclusion: These results provide the first quantitative data of drug utilization in liver disease and highlight the wide variability in prescribing practices across centers and the higher than expected use of non-evidence-based treatments, especially vitamin K and antiulcer drugs.

Keywords  
Drug utilization study · Liver cirrhosis · Anti-ulcer drugs

Introduction

Acute and chronic liver diseases are the results of various processes that encompass a wide array of clinical presentations, prognoses, and outcomes and are an important cause of morbidity and mortality among hospital inpatients. In addition, for most liver diseases there is no specific therapy for cell damage and scarring. When fibrosis ensues portal hypertension may develop, which together with a decrease in hepatic reserve, results in the three major potentially fatal complications of chronic liver disease: variceal bleeding, ascites, and encephalopathy. Although significant improvements in the management of these complications have been made in the last years, very few clear international guidelines have been published [1, 2, 3, 4, 5, 6, 7]. In addition, therapy of portal hypertension involves multiple therapeutic approaches. Thus, to prevent variceal re-bleeding pharmacological or endoscopic treatment has been demonstrated to be of benefit [2, 3, 5, 6]. Ascites can be managed with paracentesis, portal-systemic shunts, or diuretic therapy [1, 8]. Furthermore, several diuretic schedules to treat ascites have been proposed, but to date none of the alternatives have been found to be clearly superior [2, 9].

Surprisingly, in this controversial and rapidly evolving field of care no assessment has been made between
recommendations focussed on evidence-based medicine and actual medical practice, as prescribing habits are largely unknown [9, 10]. Furthermore, analysis of practice patterns is an important step to encourage quality use of medicines [11]. The aim of the present large-scale prospective multicenter study in Spain was to describe the prescription patterns of practicing physicians for patients with liver cirrhosis and to determine the extent of practice variability across participating centers, which represented up to one-fourth of the national health system.

Methods

Study design and population

A network of 25 hospitals providing specialized care for liver diseases available to an overall catchment population of 10.8 million inhabitants was set up under the methodological and operational coordination of a clinical pharmacology research unit. With the exception of patients admitted for programmed diagnostic (i.e., liver biopsy) or therapeutic (i.e., endoscopic injection sclerotherapy or band ligation of esophageal varices) procedures (as a change in the therapeutic management was not anticipated), all patients admitted to the gastrointestinal and liver units with a diagnosis of liver disease on five centrally assigned index days between February and June 1999 were included in the study. The research protocol was approved by the locally appointed ethics committee.

Data collection

In each participating hospital, the physician in charge of the study prospectively collected information on all patients with a diagnosis of liver disease that were admitted on any of the assigned days. After obtaining the consent of the patient, the physician interviewed the patient and reviewed his clinical records up to hospital discharge.

Information was collected with use of standardized and specific report forms. Admission data, including social and demographic characteristics, drinking and smoking habits, type of referral, present medical condition, severity of the disease according to Child-Pugh classification, and pharmacological treatments, were recorded. Information was obtained from the clinical records and by asking all patients about the treatment followed. Errors in the ascertainment of medicines that the patients were actually taking were minimized by using all available sources of information. Patients were questioned to identify drugs used for other medical problems not related to the liver that might not have been recorded in the medical record. In addition, family members were interviewed when patients were not able to collaborate. Medication containers, which family members or other caretakers were asked to bring to the hospital, were inspected. When a written medication plan was provided, the possibility of recall errors by the patient was reduced. Adverse drug events, defined as injuries resulting from use of a drug, were also investigated. Possible adverse drug events presented on admission were noted by the attending physician. Later, these events were evaluated by the physician in charge of the study in each center (a clinical pharmacology or a specialist) and analyzed according to an appropriate temporal sequence, exclusion of other diseases, improving with cessation, and previous knowledge of the reaction. The adverse drug events were classified according to the type of organ damage.

In-hospital information and prescriptions at discharge included diagnosis of liver and comorbid conditions (documented in the medical chart) and drugs recommended at discharge (specifying daily dose, route, and frequency of administration and diagnosis motivating the prescription), duration of follow-up, and outcome. Diagnosis of liver cirrhosis was made according to the standardized clinical, ultrasonographic, endoscopic, and histological criteria [12]. Forms were checked for completeness at the coordinating center before data entry.

Diuretic schedules

The usual diuretic combination regimen consists of oral spironolactone and furosemide at a ratio 100 mg to 40 mg. The spironolactone/furosemide ratio was calculated when applicable. A ratio equal to 1 indicated that the combination of diuretics was prescribed at a 100 mg:40 mg proportion; a ratio greater than 1 indicated a higher dose of spironolactone, while a ratio lower than 1 indicated a higher dose of furosemide.

Medical conditions were coded using the Ninth Revision of the International Classification of Diseases, Clinical Modifications. Medicines were classified according to the Anatomical Classification System (ATC) recommended by the World Health Organization Europe [13]. The overall utilization rate for the main recommended treatments was calculated as the number of patients receiving the therapy divided by the total number of patients.

Data management and statistical analysis

Data were analyzed with the Statistical Package for Social Sciences (SPSS, version 10.0) for Windows software. Variables were examined using descriptive frequencies. Bivariate associations were measured using $t$-tests or Wilcoxon rank sum tests for continuous variables and the chi-squared test for categorical items. Analysis of variance was used for comparisons of groups. Differences were reported as statistically significant if the $P$ value was less than 0.05.

Results

Five hundred and sixty-eight patients (396 men, 70%) were enrolled from 25 hospitals in nine regions. Sixteen protocols were found to have included ineligible patients or to be unsuitably coded and were therefore excluded. Mean age was 61 years (range 27–92 years). Alcoholic cirrhosis accounted for 44% (248) of the sample, viral cirrhosis represented 38% (218), and cirrhosis of unknown cause 16% (102). Patients did not differ significantly in mean age between hospitals in different regions. The prevalence of major cirrhosis complications warranting the use of the drugs under study was also comparable among centers (Table 1). There was a great variability in the mean number of drugs prescribed among regions ($P < 0.001$). Child-Pugh class A cirrhotic patients were more frequent in the Cantabria, Asturias, and Comunidad Valenciana regions, but the severity of liver disease did not account for the different utilization of drugs among regions (Table 1). Thus, in the Aragon region the worse the severity of liver disease (Child-Pugh type B–C 91%), the lower the number of drugs prescribed [1, 3], while the opposite could be seen in Asturias.

Diabetes mellitus (125 patients), infectious disorders other than spontaneous bacterial peritonitis (110 patients), gastric acid-related disorders (69 patients), chronic respiratory diseases (49 patients), heart disease (47 patients), and hypertension (45 patients) were the