Research Article

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Diabetes as a risk factor for hepatic encephalopathy in cirrhosis patients

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Background & Aims: It remains unclear whether diabetes increases the risk for hepatic encephalopathy (HE) in cirrhotic patients. We examined this question using data from three randomized trials of satavaptan, a vasopressin receptor antagonist that does not affect HE risk, in cirrhotic patients with ascites.
Methods: The trials included 1198 patients, and we excluded those with HE before or at randomization and followed the remaining patients for the one year duration of the trials. They were examined for HE regularly, and we compared rates of first-time overt HE between diabetics and non-diabetic patients using Cox regression, adjusting for gender, age, ascites severity, cirrhosis etiology, Child-Pugh class, creatinine, bilirubin, INR, sodium, potassium, albumin, platelets, lactulose use, benzodiazepine/barbiturate use, spironolactone dose, furosemide dose, potassium-sparing diuretic dose, and CirCom comorbidity score.
Results: We included 862 patients of whom 193 (22%) had diabetes. In total, they experienced 115 first-time episodes of overt HE during the follow-up. Fewer diabetics than non-diabetic patients were in Child-Pugh class C at baseline (13% *vs.* 23%), yet they had higher cumulative risk of first-time overt HE (26.0% *vs.* 15.8% after 1 year), and their episodes of first-time overt HE were more likely to progress beyond grade 2 (64% *vs.* 42% of episodes progressed to grade 3 or 4, $p = 0.01$ for independence between diabetes and highest HE grade). After the confounder adjustment, the hazard ratio of first-time overt HE for diabetics *vs.* non-diabetic patients was 1.86 (95% CI 1.20–2.87).
Conclusions: Diabetes increased the risk of first-time overt HE among cirrhotic patients with ascites.

Keywords: Hepatic encephalopathy; Cirrhosis; Diabetes mellitus; End-stage liver disease; Prognosis.
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Abbreviations: HE, Hepatic encephalopathy; NASH, non-alcoholic steatohepatitis; TIPS, transjugular intrahepatic portosystemic shunt.

Introduction

Clinically manifest hepatic encephalopathy (HE) is a very serious complication in liver cirrhosis. A marker of liver failure, its emergence is associated with an expected survival time of just a few months. Some cirrhotic patients are known to be at a greater risk of HE than others, particularly those with previous episodes, but also those with hyponatremia, poor metabolic liver function [1], or a transjugular intrahepatic portosystemic shunt (TIPS). In addition, diabetes mellitus has also been associated with a higher prevalence of HE [2–5], although findings are not consistent [6]. Moreover, all previous studies addressing this question used a cross-sectional study design, meaning that they could not determine whether diabetes increased the incidence or the duration of HE episodes. Diabetes has never been examined as a risk factor for HE in a cohort study design.

There are good reasons to believe that diabetes favors HE development. Ammonia is taken to be the first hit in HE development, and diabetes induces glutaminase which via deamidation of glutamine releases ammonia [7]. Moreover, the insulin resistance inherent in cirrhotic diabetes favors muscle breakdown and ammonia production [7]. Diabetes may also increase bacterial translocation from the gut both by prolonging the intestinal transit time and causing bacterial overgrowth [8], and by modifying the gut microbiome [9]. This may lead to systemic inflammation, one of the most important second hits in HE development [10].

We had access to the complete original data from three randomized controlled trials of satavaptan treatment of ascites in patients with cirrhosis. Satavaptan, a vasopressin receptor antagonist, had no effect on the development of HE [11]. During the one year follow-up in these trials the participants were clinically examined for HE regularly, and their comorbidities, medications, and blood chemistry were recorded [12]. The aim of this analysis of the trial data was to examine whether diabetes increases the risk of first-time overt HE in cirrhotic patients with ascites.

Patients and methods

Between July 2006 and December 2008 three multinational randomized controlled trials were conducted to examine whether satavaptan was efficacious in treating ascites in cirrhotic patients. The three trials were conducted similarly but had different target populations: patients with diuretic-manageable ascites

(N = 462), patients with ascites managed with diuretics and occasional therapeutic paracentesis (N = 496), and patients with diuretic-resistant ascites managed primarily with therapeutic paracentesis (N = 240). In the first trial, the primary outcome was worsening of ascites, in the other two it was the cumulative number of large volume paracenteses during 12 weeks [12]. Patients with a functioning TIPS were excluded, as were patients with variceal bleeding or spontaneous bacterial peritonitis in the 10 days before randomization. Other reasons for exclusion were: serum creatinine >151 μmol/L, serum potassium ⩾5.0 mmol/L, serum sodium >143 mmol/L, serum bilirubin >150 μmol/L, international normalized ratio (INR) >3.0, platelets <30 * 10^9/L, neutrophils <1 * 10^9/L, hepatocellular carcinoma exceeding the Milan criteria, use of a potent modifier of the cytochrome P450 3A drug metabolism pathway, or use of drugs that increase the risk of Q-T interval prolongation [12].

The risk factors for first-time development of HE may be different from the risk factors for recurrence of HE or progression of HE, and our interest was in first-time development. Therefore we excluded those of the 1198 trial participants who had previously had an HE episode (N = 306) or had HE at the time of randomization (N = 26). We also excluded those patients who had no recorded Child-Pugh class (N = 3) or serum biochemistry (N = 1).

Study design

The planned treatment duration was 52 weeks, but the second and third trials were stopped early due to a poor risk-benefit ratio [12]. All who were still receiving study medication at this time were followed for one additional week to assess drug safety, and we considered them study completers. In all three trials some patients discontinued treatment before study completion, primarily due to adverse events. Irrespective of the reason for discontinuation, these patients were also followed for one additional week to assess drug safety. Any patient who experienced an adverse event was followed until the event resolved or stabilized, so follow-up in the trials could extend far beyond the planned 52 + 1 weeks. For the analysis presented here, however, we stopped follow-up on the date of the drug safety assessment, or earlier, as described below.

Data collection

Data on diabetes including its type and treatment were collected at the time of randomization, but the study protocol did not give explicit criteria for the diagnosis of diabetes. During the follow-up, patients were seen every four weeks in their hepatology departments, and at those visits all current medications including their indications and dosages were recorded, and blood tests were taken. All clinical events during the follow-up were recorded.

Data on HE episodes were recorded as part of the safety assessment, and every four-week visit included a systematic examination for signs and symptoms of HE by an experienced clinician and a history of HE episodes since the previous visit. There was no psychometric testing for minimal HE. For every HE episode the clinician recorded the severity according to the West Haven criteria [13], the dates of onset and resolution, and likely precipitating factors. When no precipitant was recorded we considered any adverse event or change in medication during the week before the HE episode as potential precipitant and we reviewed the safety data in search of the most plausible one. Finally, we categorized the precipitating factors in accordance with the newly published international guidelines, so that HE was due to one of the following: infection, gastrointestinal bleeding, diuretic overdose, electrolyte disorder, constipation, or unidentified cause [13]. We added an 'other' category for precipitants that did not fit any of these categories. If the precipitant was reported as dehydration or renal failure, we categorized it as 'electrolyte disorder'.

Statistical analysis

Follow-up began at randomization and ended when one of the following events occurred: a first-time episode of overt HE (West Haven grade 2, 3, or 4), death, or the safety follow-up date following study completion or premature discontinuation of treatment. We used the Mann-Whitney test (for age and biochemistry) and the chi-square test (for other characteristics) to test whether the diabetic and non-diabetic patients were identical at study entry or at their first episode of overt HE.

The cumulative risk of first-time overt HE for patients with or without diabetes was estimated using the cumulative incidence function, treating death as a competing outcome event, and study completion and premature treatment discontinuation as censoring events [14]. Censoring was likely to depend on cirrhosis severity, because development of complications of cirrhosis or other adverse events might result in premature treatment discontinuation. We therefore corrected the estimates of cumulative risk for that dependency using inverse probability of censoring weights [15]. Those weights were obtained from a Cox regression model including patient gender, age, diabetes, ascites severity (diuretic-manageable [reference value], occasional therapeutic paracentesis, or primarily therapeutic paracentesis), and serum creatinine, bilirubin, INR, and sodium.

We used Cox proportional hazards regression to examine the effects of diabetes on the hazard rate of first-time overt HE. We adjusted for confounding by patient gender, age, ascites severity, cirrhosis etiology (alcohol only [reference value], chronic hepatitis B only, chronic hepatitis C only, non-alcoholic steatohepatitis [NASH] only or cryptogenic cirrhosis, or other etiology); Child-Pugh class (A [reference value], B, or C); serum creatinine, bilirubin, INR, sodium, potassium, albumin, and platelets; lactulose and benzodiazepine/barbiturate use (yes or no, regardless of dose and indication); spironolactone dose, furosemide dose, and potassium-sparing diuretic dose; and CirCom score. The CirCom score is a comorbidity index specifically designed to predict mortality among cirrhotic patients [16]. It consists of two variables: one has a value of 0, 1, 3, or 5 depending on a patient's most severe comorbidity; the other has a value of 0 or 1 depending on whether a patient has more than one comorbid disease. The CirCom comorbidities are cancer, chronic kidney disease, acute myocardial infarction, heart failure, peripheral arterial disease, chronic obstructive lung disease, epilepsy, and substance abuse other than alcoholism. In the Cox model, age, biochemistry, and diuretic dose were included as continuous, linear variables, and all variables were updated during the follow-up. Patients' Child-Pugh score was reported by the clinicians who were not given specific instructions how to define mild ascites (2 points) as opposed to moderate ascites (3 points).

In a second analysis, we stratified patients based on whether they were currently using lactulose. This was done because lactulose may have been a marker of minimal HE. Patients started or stopped lactulose treatment during the follow-up, so some patients contributed follow-up time to both lactulose strata.

In a third analysis, we divided the diabetes patients into four groups according to their antidiabetic treatment at study entry: insulin, metformin, another oral antidiabetic, or diet alone. In this analysis, diabetes was included in the Cox model as a categorical variable, and we included the same confounding variables as in the first analysis.

In a fourth analysis, we included only the diabetic cirrhotic patients and examined the current fasting blood glucose level as a risk factor for HE development. Blood glucose was categorized as hypoglycemia (<4 mmol/L), euglycemia (4 to 9.9 mmol/L), or hyperglycemia (⩾10 mmol/L). Hemoglobin A1c was not measured. This analysis included the same confounders as the primary analysis.

In a fifth analysis, we excluded all patients with cancer at the time of study entry. This was done because cancer may stimulate the glutaminase activity [17]. The analysis was otherwise the same as the first Cox regression analysis and included the same confounders.

In a sixth analysis, we redefined HE episodes to include grade 1, i.e. follow-up ended when one of the following events occurred: a first-time episode of HE (West Haven grade 1, 2, 3, or 4), death, or the safety follow-up date following study completion or premature discontinuation of treatment. The Cox regression analysis was the same as in the first analysis and included the same confounders.

Results

We analyzed data from 862 cirrhotic patients, and 193 (22%) had diabetes, nearly all (96%) of type 2. Of the diabetic patients, 85 (44%) were treated with insulin, 25 (13%) with metformin, 36 (19%) with another oral antidiabetic drug, and 47 (24%) with diet alone. At study entry, 31% of patients had a serum sodium <135 mmol/L, and 7% <130 mmol/L. The total duration of follow-up was 539.4 person-years, with a median of 240 days per patient. During one year of follow-up 115 patients developed overt HE (there was one first-time overt HE episode per 4.7 person-years), 43 died (one death before first-time overt HE per 13.0 person-years), and 302 stopped treatment prematurely (one premature treatment discontinuation per 1.8 person-years).

More diabetic patients had NASH cirrhosis (18% *vs.* 5%), and diabetic patients had better liver status at study entry with 13% *vs.* 23% in Child-Pugh class C (Table 1). Their MELD scores were the same because their better bilirubin and INR values were balanced by their worse kidney function (median creatinine 86 *vs.* 75 μmol/L), and 10% of the diabetics *vs.* 4% of the non-diabetic