Research Article

JOURNAL OF HEPATOLOGY

Correction of hyponatraemia improves cognition, quality of life, and brain oedema in cirrhosis

Vishwadeep Ahluwalia[1,2], Douglas M. Heuman[1], George Feldman[3], James B. Wade[4], Leroy R. Thacker[5], Edith Gavis[1], HoChong Gilles[1], Ariel Unser[1], Melanie B. White[1], Jasmohan S. Bajaj[1,*]

[1]*Department of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, VA, USA;* [2]*Department of Radiology, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, VA, USA;* [3]*Department of Nephrology, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, VA, USA;* [4]*Department of Psychiatry, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, VA, USA;* [5]*Department of Biostatistics, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, VA, USA*

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Background & Aims: Hyponatraemia in cirrhosis is associated with impaired cognition and poor health-related quality of life (HRQOL). However, the benefit of hyponatraemia correction is unclear. The aim of this study was to evaluate the effect of tolvaptan on serum sodium (Na), cognition, HRQOL, companion burden, and brain MRI (volumetrics, spectroscopy, and diffusion tensor imaging) in cirrhotics with hyponatraemia.

Methods: Cirrhotics with Na <130 mEq/L were included for a four-week trial. At screening, patients underwent cognitive and HRQOL testing, serum/urine chemistries and companion burden assessment. Patients then underwent fluid restriction and diuretic withdrawal for two weeks after which cognitive tests were repeated. If Na was still <130 mEq/L, brain magnetic resonance imaging (MRI) was performed and tolvaptan was initiated for 14 days with frequent clinical/laboratory monitoring. After 14 days of tolvaptan, all tests were repeated. Comparisons were made between screen, pre-and post-drug periods Na, urine/serum laboratories, cognition, HRQOL and companion burden.

Results: 24 cirrhotics were enrolled; seven normalized Na without tolvaptan with improvement in cognition. The remaining 17 received tolvaptan of which 14 completed the study over 13 ± 2 days (age 58 ± 6 years, MELD 17, 55% HCV, median 26 mg/day of tolvaptan). Serum Na and urine free water clearance increased with tolvaptan without changes in mental status or liver function. Cognitive function, HRQOL and companion burden only improved in these 14 patients after tolvaptan, along with reduced total brain and white matter volume, increase in choline on magnetic resonance spectroscopy, and reduced cytotoxic oedema.

Conclusions: Short-term tolvaptan therapy is well tolerated in cirrhosis. Hyponatraemia correction is associated with cognitive, HRQOL, brain MRI and companion burden improvement.

Introduction

Hyponatraemia, which reflects systemic haemodynamic derangement due to systemic vasodilatation and renal water retention, is associated with poor outcomes in cirrhosis [1]. These adverse outcomes include impaired cognition, reduced health-related quality of life (HRQOL) and a complicated post-transplant course [2–4]. Interventions such as fluid restriction, diuretic withdrawal and aquaretic agents like tolvaptan can improve serum sodium without correcting the underlying haemodynamic derangement [5]. However, it is unclear to what extent the clinically relevant morbidity associated with hyponatraemia such as impaired cognition and HRQOL, increased companion burden and brain MR functioning can be improved by correcting serum sodium. Our aim was to study the effect of sodium correction on cognitive function and its effect on patients' (HRQOL and brain MRI) and their companions' burden.

Keywords: Caregiver burden; Aquaresis; Diffusion tensor imaging; Hepatic encephalopathy; Magnetic resonance spectroscopy; Tolvaptan.
Received 12 May 2014; received in revised form 21 June 2014; accepted 23 July 2014; available online 8 August 2014
☆ DOI of original article: http://dx.doi.org/10.1016/j.jhep.2014.09.028.
* Corresponding author. Address: Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University and McGuire VA Medical Center, 1201 Broad Rock Boulevard, Richmond, VA 23221, USA. Tel.: +1 804 675 5021; fax: +1 804 675 5816.
E-mail address: jsbajaj@vcu.edu (J.S. Bajaj).
Abbreviations: HRQOL, health-related quality of life; HE, hepatic encephalopathy; SIADH, syndrome of inappropriate ADH secretion; MMSE, mini-mental status exam; NCT-A/B, number connection test A/B; DST, digit symbol test; BDT, block design test; SDT, serial dotting test; LTT, line tracing test; ICT, inhibitory control test; PHES, psychometric hepatic encephalopathy score; CLDQ, chronic liver disease questionnaire; PCB, perceived caregiver burden; TWA, time-weighted average; AUC, area under the curve; DTI, diffusion tensor imaging; FA, fractional anisotropy; CS, spherical isotropy; MD, mean diffusivity; Cho, choline; Cr, creatine; mI, myo-inositol; Glx, glutamate + glutamine.

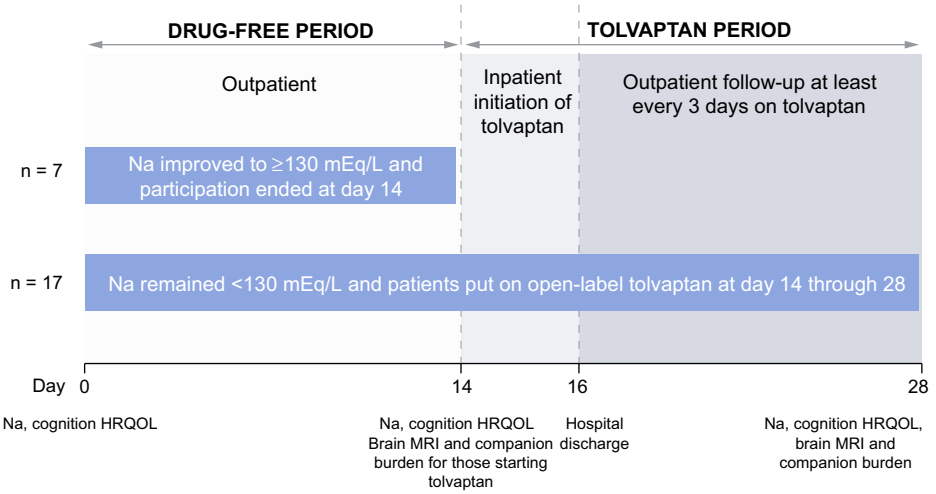

Fig. 1. Schema of the study design. (This figure appears in colour on the web.)

Patients and methods

Patients

We recruited outpatients with cirrhosis (based on histology, radiology, varices on endoscopy or suggestive laboratory features [platelets <150,000 with an AST/ALT ratio >1 in chronic liver disease] and with a serum sodium <130 mg/dl within the last 14 days) from the McGuire VA and VCU Medical Centers. Patients had to have a companion and able to undergo brain MRI. We included patients with prior HE, provided they had a mini-mental status exam (MMSE) >25, their last hepatic encephalopathy (HE) episode was >2 months prior to enrolment and they had suffered <2 episodes within the last 6 months.

We excluded patients who were abusing alcohol/illicit drugs within the last 3 months, those with psychoactive drug use other than regularly scheduled anti-depressants, other causes of hyponatraemia (congestive heart failure, SIADH, etc.), hypovolemia, TIPS, HIV infection, pregnant patients, those on azole medications, on therapies other than simple fluid restriction or diuretic withdrawal for hyponatraemia (vaptan use or hypertonic saline) in the last month and those who were unable to provide consent. The study is registered at www.clinicalstrials.gov NCT0155664 and the overall schema is shown in Fig. 1.

Screening visit

If patient Na was <130 mEq/L, the patient was included; procedures performed were: (a) history of cirrhosis complications, fluid intake and diuretic use; (b) physical examination to exclude overt HE (asterixis, modified-orientation log and MMSE) [6]; (c) blood drawn for electrolytes (Na, K, Mg, P), renal function (creatinine, blood urea nitrogen), hepatic function (albumin and MELD score) and venous ammonia; (d) cognitive tests; and (e) HRQOL, measured with the Chronic Liver Disease Questionnaire (CLDQ) [7]. Cognitive tests used were: the number connection tests A and B (NCT-A/B), digit symbol test (DST), block design test (BDT), line tracing test (errors and time, LTT e/t), serial dotting test (SDT) and inhibitory control tests (ICT lures and targets%) [8]. Different versions of the paper-pencil tests were used at each visit to reduce learning. The psychometric hepatic encephalopathy score (PHES) was calculated; a PHES >−5 standard deviations was considered impaired while the others were considered to have normal cognition [9]. The companions were asked formally about their relationship details with the patient and underwent a validated questionnaire, the perceived caregiver burden (PCB) [10].

At the end of the screening visit, the patients were instructed to restrict their fluid intake to 1.5 L/day and their diuretics were withdrawn or reduced as tolerated. Patients were asked to collect their 24 h urine for the day prior to the pre-drug visit for which they were seen at day 14.

Pre-drug visit

Patients were then seen with their companions and underwent a serum sodium assessment, questioning regarding fluid and diuretic restriction and cognitive testing. If the serum sodium was ⩾130 mEq/L, they were not started on tolvaptan and they underwent a Na draw 14 days later. For the remainder, screening visit procedures were repeated, brain MRI performed (details after study design). The 24-h urinary collection pre-drug was analysed for volume, osmolality and measured values of sodium (Na) and potassium (K). Companions again completed the PCB questionnaire. Blood was also collected for renin and copeptin measurement (performed at AssayGate, MD).

Inpatient tolvaptan study

Tolvaptan was initiated at 15 mg for the first dose. All intake and output was charted, all urine was collected, and a 24 h urinary collection for the electrolytes mentioned above was performed daily. Study staff was present with the patient throughout. Serum sodium and mental status were analysed every 8 h. Patients were allowed to drink water per thirst. Daily physical examination by study doctors and laboratory evaluation of renal and hepatic function were performed. If sodium levels rose by ⩽8 mEq/L over 24 h while the patient was at 15 mg dosage, it was advanced to 30 mg/day which was the maximum dose. After 72 h, patients were discharged with their assigned tolvaptan doses for a follow-up within 3 days.

Outpatient drug follow-up

Patients and companions were followed every 3–5 days for at least 4 outpatient visits till the end-of-drug visit. During each visit, tolerability and use of tolvaptan (history/pill count), use of other medications, fluid intake and urine output, and adverse events were inquired, a physical examination was performed and blood electrolytes, venous ammonia, renal and hepatic function were assessed. Patients and companions were then continued in the study till the end-of-drug visit. At any point, if the serum sodium increased to ⩾140 mEq/L, the drug was held till the next visit.

End-of-drug visit

At day 14, patients and companions underwent all tests and procedures that were performed at drug initiation. The final pill count was performed and the study participation was terminated.