Research Article

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Predictors of response to terlipressin plus albumin in hepatorenal syndrome (HRS) type 1: Relationship of serum creatinine to hemodynamics

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Background & Aims: Administration of terlipressin plus albumin is effective in reversing type 1 HRS as compared to albumin alone. However, only about 1/3 of patients respond to treatment, therefore, predictors of response and survival would help identify the patients most likely to benefit from treatment.

Methods: We analyzed our controlled trial of terlipressin *vs.* placebo (*Gastroenterology* 2008;134:1360) to define factors predictive of a response and to correlate hemodynamic changes to changes in renal function.

Results: Single variant analysis showed treatment with terlipressin, MELD score, and baseline serum creatinine to be predictive of HRS reversal. Alcoholic hepatitis, baseline serum creatinine, and MELD score were predictive of survival. When treatment was not considered as a variable, only baseline serum creatinine predicted HRS reversal. Baseline serum creatinine, presence of alcoholic hepatitis, and Child-Pugh score were also predictive of survival on multivariate analysis. The rise in mean arterial pressure (MAP) following terlipressin administration was not predictive of HRS reversal. However, in those who achieved HRS reversal from terlipressin, there was a significant rise in MAP from beginning to end of treatment.

Conclusions: The most consistent predictor of response to terlipressin and of survival is the baseline serum creatinine. Patients most likely to benefit from terlipressin have earlier onset renal failure (i.e. serum creatinine <5.0 mg/dl). A sustained rise in MAP is required for HRS reversal. As MAP is a surrogate marker for the hyperdynamic circulation, it is only with improvement in the hyperdynamic circulation that HRS reversal is observed.

Introduction

Hepatorenal syndrome (HRS) type 1 is a rapidly progressive but potentially reversible form of renal failure that occurs in patients with cirrhosis and ascites and is associated with high mortality [1–3]. The main pathophysiological basis for the development of HRS type 1 is the progressive systemic arterial vasodilation. Arterial vasodilation, especially in the splanchnic bed, leads to a decrease in effective arterial blood volume with subsequent activation of renal sodium-retentive mechanisms and intrarenal arterial vasoconstriction. As the hyperdynamic circulation worsens, there is a progressive intrarenal arterial vasoconstriction leading to renal failure in the absence of intrinsic kidney disease [4–7].

Appreciation of the central role of arterial vasodilation in the pathogenesis of HRS has led to the use of arterial vasoconstrictors for its treatment. A number of vasoconstrictors including terlipressin, ornipressin, midodrine plus octreotide, and norepinephrine have been used in HRS type 1 [2,3,7–10]. Terlipressin, a 12 amino acid synthetic analog of lysine-vasopressin, is the most widely used drug for the treatment of HRS and three randomized controlled trials have compared terlipressin plus albumin to albumin alone [8–10]. In the largest and only placebo-controlled multicenter trial, HRS reversal was observed in 34% of the terlipressin treated patients and 13% of those receiving placebo ($p = 0.008$) [8]. In a recent systematic analysis of vasoconstrictors for HRS, terlipressin plus albumin was significantly more likely to reverse HRS and also to improve short term survival as compared to albumin alone [11].

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Abbreviations: HRS, hepatorenal syndrome; MELD, model for end-stage liver disease; MAP, mean arterial pressure; SCr, serum creatinine; CI, confidence intervals; EOT, end of treatment.

Given the fact that terlipressin has the side-effects expected of a V_1-mediated vasoconstrictor, it would be preferable to restrict exposure to the patient group most likely to respond to treatment. We examined the variables predictive of a response to terlipressin plus albumin and albumin alone in the treatment of HRS type 1 in our previously published randomized controlled trial [8]. We wanted to better define the population of patients most likely to benefit from treatment with terlipressin. We also hypothesized that mean arterial pressure (MAP) was a surrogate marker of the hyperdynamic circulation, and if terlipressin caused a consistent rise in MAP and that rise was associated with an improvement in renal function, then terlipressin would be working by improving the hyperdynamic circulation. Therefore, by examining the hemodynamic response to terlipressin plus albumin *vs.* albumin alone in the same patients, we hoped to gain a better understanding of how terlipressin reverses renal failure in patients with type 1 HRS. The results of these analyses are the subject of this report.

Materials and methods

Patients and study design

Adult subjects ($\geqslant$18 years of age) with acute or chronic liver disease and HRS type 1, as defined by the International Ascites Club criteria (rapidly progressive reduction in renal function, e.g., doubling of serum creatinine (SCr) to $\geqslant$2.5 mg/dl in less than two weeks, and failure of renal function to improve following diuretic withdrawal and plasma volume expansion) [12] were included in this trial which has been described in detail [8]. The study was a prospective, randomized, double-blind, placebo-controlled, multicenter clinical trial conducted at 35 medical centers across the United States (n = 30), Germany (n = 2), and Russia (n = 3) from 2004 through 2006. The study was registered in the national clinical trials database (ClinicalTrials.gov identifier NCT00089570) and approved by the institutional review boards at each center. All data were recorded on standardized case report forms that were entered into a database at a data coordinating center.

Subjects with acute or chronic liver disease and acute worsening of renal function were initially screened for the study. The diagnosis of alcoholic hepatitis was made by the investigator at the site at the time of enrollment and was based on clinical criteria as a liver biopsy was not required. Following randomization, patients received blinded study medication either terlipressin at a dose of 1 mg administered by slow intravenous (IV) push every 6 h or matching placebo. Most of the patients (88%) also received intravenous albumin [8]. Serum electrolytes, BUN, and creatinine were evaluated daily during treatment. Concomitant medications were recorded. MAP was measured immediately before and 2 h after each dose of the study drug, to correspond with peak effect of terlipressin, and the mean value for each day was calculated.

Statistical analysis

All analyses conducted for this report used all patients in the ITT population who received at least one dose of the study drug (56 patients on terlipressin and 55 on placebo) unless otherwise stated. When analyses were conducted by treatment arm, this was explicitly mentioned. Key analyses presented were prospectively planned, with additional exploratory analyses performed retrospectively.

Univariate and multivariate logistic regression analyses were conducted to determine baseline patient characteristics that were predictive of HRS reversal (defined as serum creatinine on treatment $\leqslant$1.5 mg/dl) and overall survival up to day 180. For HRS reversal Wald Chi-Square Tests and relative risks from a single logistic regression were used, both with and without treatment as a factor. For survival, log-rank tests for association were used. The following factors were used for univariate analysis and a subgroup of these for multivariate analysis: age group (<65, $\geqslant$65), gender (M *vs.* F), race group (non-white, white), alcoholic hepatitis (present *vs.* not), baseline MELD score, Child-Pugh score, MAP, serum sodium, bilirubin, and creatinine (SCr). Median values and confidence intervals (CI) were determined as appropriate. SAS® software version 8.2 was used to perform all statistical analyses and to prepare summary tables and data listings. The protocol provided for descriptive subgroup and correlative analyses, included the univariate analysis and in-depth examination of the MAP data. There was also a provision for unspecified exploratory analyses. The multivariate analysis was thus performed retrospectively, as was the plotting of MAP *vs.* serum creatinine by response group, as well as the beta-blocker and the renal function subgroup analyses.

Results

Predictors of HRS reversal and survival

HRS reversal was seen in 19/56 terlipressin treated patients and 7/56 placebo patients. The only variables that were significantly different by single variant analysis between those with and without HRS reversal were MELD score, treatment group, and baseline SCr. For overall survival, univariate predictors of outcome were alcoholic hepatitis, SCr and MELD, with Child-Pugh and baseline bilirubin showing non-significant trends (Table 1). We conducted multivariate analyses to verify the independent influence of these factors on HRS reversal. When treatment was considered in the analysis, due to the strength of this effect on HRS reversal, treat-

Table 1. Summary of the effects of baseline characteristics on HRS reversal and survival (univariate analysis, ITT population).

Baseline parameter	HRS Reversal			Survival		
	RR	95% CI	*p* value	RR	95% CI	*p* value
Treatment group	2.71	1.24-5.94	0.009	0.93	0.58-1.51	0.782
Alcoholic hepatitis	0.97	0.49-1.92	0.890	2.29	1.41-3.72	<0.001
Gender	0.57	0.31-1.08	0.055	1.00	0.59-1.69	0.963
MELD score	0.95	0.91-0.99	0.017	1.05	1.01-1.10	0.030
Child-Pugh score	0.87	0.75-1.02	0.065	1.15	1.00-1.32	0.051
Serum creatinine	0.65	0.46-0.93	0.021	1.40	1.22-1.60	<0.001
Bilirubin	1.00	0.97-1.02	0.805	1.01	1.00-1.03	0.087
MAP	0.99	0.96-1.02	0.459	1.02	0.99-1.04	0.216
Serum sodium	0.99	0.95-1.04	0.730	0.99	0.95-1.03	0.519

RR: relative risk; 95% CI: 95% confidence intervals.