Journal of Cardiology xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Comparison of two dosing methods for immediate administration of tolvaptan in acute decompensated heart failure

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ARTICLE INFO

Article history:
Received 26 December 2017
Received in revised form 6 February 2018
Accepted 8 February 2018
Available online xxx

Keywords:
Heart failure
Dosing methods
Congestion score

ABSTRACT

Background: The clinical dosing method for tolvaptan in patients with acute heart failure (HF) is still unclear. We aimed to compare the differences in clinical effect between two dosing regimens: once-daily 7.5 mg and twice-daily 3.75 mg.
Methods: In this randomized trial, tolvaptan was administered within 12 h from hospital admission. The primary outcome was the serial change in congestion scores measured every day from enrollment until dosing day 7. Outcomes including safety parameters were also evaluated.
Results: The subjects were assigned to either the once-daily 7.5 mg dosing regimen ($N = 15$) or the twice-daily 3.75 mg dosing regimen ($N = 16$). The time-course changes in body weight, serum sodium and creatinine levels, systolic blood pressure, daily urine output, and congestion scores were similar between the two groups. In the twice-daily 3.75 mg dosing group, the serum sodium levels on days 3 and 4 were significantly ($p < 0.05$) increased compared with those on day 1. The congestion scores significantly ($p < 0.05$) decreased from day 2 to day 7 in both groups compared with those on day 1. However, the difference in the serial change in the congestion scores did not reach statistical significance.
Conclusions: Our present results suggest that the early administration of tolvaptan within 12 h after hospital admission significantly improved congestion from the first day after administration by either dosing regimen, i.e. once-daily 7.5 mg or twice-daily 3.75 mg in patients with acute HF.

Introduction

As the incidence of heart failure (HF) is rapidly increasing in developed countries, its great social importance is increasingly being recognized [1]. According to contemporary epidemiological data, the prevalence of HF may increase by 90,000 every 5 years in Japan [2]. Given the worsening prognosis in terms of re-hospitalization for HF, appropriate and continuous approaches will be necessary in the management of this condition.

Loop diuretics are indispensable in the treatment of HF with volume overload. Although an effective diuresis can be attained in most patients with loop diuretics, various adverse effects including renal function loss, hypotension, and serum electrolyte imbalance sometimes occur [3]. Among them, acute renal function loss is one of the worsening prognostic factors in patients with acute decompensated HF [4–6]. Therefore, diuretic therapy should be provided as much as possible to retain renal function. Despite the therapeutic strategies with loop diuretics, the most appropriate strategy for achieving decongestion, a chief management strategy for patients with HF, remains to be elucidated [7].

Tolvaptan, an orally active arginine vasopressin V2 receptor antagonist, inhibits vasopressin-mediated water reabsorption in the renal collecting ducts without increasing urine electrolyte excretion [8]. Moreover, it is sometimes used for worsening HF in

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https://doi.org/10.1016/j.jjcc.2018.02.006
0914-5087/

addition to other diuretics including loop diuretics. Clinical studies on HF have reported that tolvaptan contributed to promoting water retention without causing electrolyte abnormalities or worsening renal function [9–11]. From the view point of pharmacokinetics and pharmacodynamics, the responses to 15 mg twice-daily regimen and 30 mg once-daily regimen had been similar [12]. Subsequent clinical trials compared the 30 mg once-daily dose with placebo [10], and the package insert information of tolvaptan from the Ministry of Health, Labour and Welfare of Japan specified this regimen. The clinical effect of this drug is expected to increase with the plurality of dosing because of its relatively short half-life in plasma; however, its clinical dosing remains unclear. Thus, we performed the present study to compare any differences in clinical and adverse effects between two dosing regimens (once-daily 7.5 mg and twice-daily 3.75 mg) in patients hospitalized for acute decompensated HF.

Materials and methods

Study population

In this multicenter randomized trial, recruitment was started in January 2016 during a 1-year period in two tertiary medical centers (Kasugai Municipal Hospital and Japanese Red Cross Nagoya Daiichi Hospital) in Aichi, Japan. The study population was randomized into two groups: one group to receive tolvaptan 7.5 mg once-daily in the morning (9 AM) [QD (quaque die) group] and the other group to receive tolvaptan 3.75 mg twice-daily (9 AM and 3 PM) [BID (bis in die) group], at a 1:1 ratio. We considered the post-marketing surveillance in Japan [13] to ensure safety in deciding the initial dose of tolvaptan in our study. The eligibility inclusion criteria for this study were as follows: unscheduled admission because of acute decompensated HF [New York Heart Association (NYHA) functional classification III or IV], complicated volume overload, scheduled tolvaptan administration within 12 h from hospital admission, and previous administration of furosemide $\geq$40 mg/day. Subjects receiving therapy with fasting, those undergoing mechanical respiratory therapy, and those who were previously or currently treated with tolvaptan were excluded from the study. We also excluded subjects undergoing hemodialysis and those with HF caused by acute myocardial infarction. The primary outcome of the study was the serial change in congestion scores measured every day from enrollment until dosing day 7. The secondary outcomes included serial changes in body weight, serum sodium level, renal function, systolic blood pressure, and urine output for 7 consecutive days after administration, and the ratio of all-cause mortality or rehospitalization for HF at 30 and 180 days. The congestion scores, body weight, serum sodium level, renal function, and systolic blood pressure were obtained early in the morning (7–9 AM) in both groups. On the first dosing day (day 1), these values were obtained before tolvaptan administration, whereas daily urine output for 24 h was gathered before and after tolvaptan administration. The study protocol complied with the Declaration of Helsinki and was approved by the Committees on Ethics of Kasugai Municipal Hospital and Japanese Red Cross Nagoya Daiichi Hospital. Written informed consent was obtained from each subject. The study was registered at University Hospital Medical Information Network Clinical Trials Registry, with the identifier UMIN000021110. Although the study protocol was approved by the Committees on Ethics of two hospitals, samples fulfilled with all inclusion criteria and obtained written informed consent were present only in Kasugai Municipal Hospital. Furthermore, because of slow recruitment rates, it became apparent that it would not be possible to recruit 50 patients within the study period.

Definition

HF was defined according to American College of Cardiology Foundation/American Heart Association guidelines with the signs and symptoms of HF, and confirmed left ventricular systolic or diastolic dysfunction [14]. The congestion score was determined according to the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcomes Study with Tolvaptan) trial, and consists of signs and symptoms including dyspnea, fatigue, orthopnea, jugular venous distention, rales, and pedal edema [15]. The congestion score was evaluated using a four-point scale ranging from 0 to 3 for each value, and calculated by summing each score. We assessed this score once a day from enrollment until dosing day 7. Because of early administration of tolvaptan within 12 h from hospital admission in the present study, baseline daily urine output before tolvaptan administration was not obtained over 12 h. We therefore calculated the predictors of the responder to tolvaptan according to the report from Imamura et al.: baseline urine osmolality $>$ 352 mOsm/L and/or % decrease in urine osmolality $>$ 26% at 4 h after tolvaptan administration [16].

Data collection

Clinical characteristics (age, sex, height, weight, previous medical history, NYHA functional classification, etiology of HF, non-cardiac comorbidities, vital signs, and laboratory data), in-hospital treatment, medications at discharge, and 30-day and 180-day outcomes (including mortality and rehospitalization for HF) were assessed. The urine osmolality was measured in 14 patients in the QD group and in all 16 patients in the BID group, and obtained on day 1 (before administration and 4 h after administration). Echocardiographic data at discharge were also collected.

Statistical analysis

Categorical variables were assessed as percentages and continuous variables as medians with interquartile range (IQR), or as mean $\pm$ standard deviation. Categorical variables were compared between the two groups with Fisher's exact test. Continuous variables were compared using the unpaired Student's *t*-test (for normally distributed variables) or Mann–Whitney *U*-test (for other variables). Changes in body weight, serum sodium level, serum creatinine level, systolic blood pressure, daily urine volume, and congestion scores were assessed using two-way repeated measures analysis of variance and paired *t*-test. To compensate for multiple comparisons of variables, we applied Bonferroni's correction for the statistical significance of associations. Given that each variable was measured for 6 days after tolvaptan administration, a *p*-value of $<$0.008 (0.05/6) was considered statistically significant. Statistical significance was examined using two-sided tests performed with JMP version 5.1 software (SAS Institute, Cary, NC, USA).

Results

The characteristics of the subjects ($N = 31$) are shown in Table 1. All subjects received loop diuretics at hospital admission and there was no difference in furosemide-equivalent dose between the two groups. Ten subjects in the QD group and thirteen subjects in the BID group required change in tolvaptan dose, and the median dose was 7.5 (IQR7.5–15) mg in both groups. In addition, seven subjects in each group were required to receive the maximum tolvaptan dose of 15 mg/day. The average age was significantly ($p < 0.05$) greater, whereas the proportion of patients with previous hospitalization was significantly smaller in the BID group.

Please cite this article in press as: Oguri M, et al. Comparison of two dosing methods for immediate administration of tolvaptan in acute decompensated heart failure. J Cardiol (2018), https://doi.org/10.1016/j.jjcc.2018.02.006