BRIEF REPORT

Comparison of the Effects of Combination Diuretic Therapy with Oral Hydrochlorothiazide or Intravenous Chlorothiazide in Patients Receiving Intravenous Furosemide Therapy for the Treatment of Heart Failure

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Study Objective To compare the effects of combination diuretic therapy with oral hydrochlorothiazide or intravenous chlorothiazide added to background intravenous loop diuretic therapy among patients hospitalized with heart failure.

Design Single-center, retrospective review.

Setting Cardiovascular hospital within a university-affiliated teaching institution.

Patients Eighty-two patients hospitalized for heart failure between September 1, 2009, and August 31, 2011, who were receiving background intravenous furosemide therapy (total daily dose ≥ 160 mg); of those patients, 28 patients also received oral hydrochlorothiazide (median dose 25 mg [interquartile range 25–50 mg]), and 54 patients also received intravenous chlorothiazide (median dose 500 mg [interquartile range 250–750 mg]).

Measurements and Main Results The primary outcome was change in 24-hour urine output. Urine output was recorded from the 24 hours before and after the first administration of either oral hydrochlorothiazide or intravenous chlorothiazide. Baseline characteristics, with the exception of female sex (p=0.01) and home loop diuretic dose (p=0.03), were similar between groups. Twenty-four–hour urine output before administration of the thiazide diuretic was not significantly different between groups. After treatment, 24-hour urine output increased in both groups; however, urine output increased to a lesser extent with oral hydrochlorothiazide (from mean ± SD 2104 ± 830 ml to 3038 ± 917 ml) than with intravenous chlorothiazide (from 2342 ± 978 ml to 4128 ± 1755 ml) (p=0.005). Hypokalemia occurred frequently in both groups: 71.4% and 83.3% in the oral hydrochlorothiazide and intravenous chlorothiazide groups, respectively (p=0.21).

Conclusion Among hospitalized patients with heart failure receiving intravenous loop diuretics, the addition of either oral hydrochlorothiazide or intravenous chlorothiazide augmented diuresis. Urine output increased to a greater extent with intravenous chlorothiazide compared with oral hydrochlorothiazide. However, given the positive response observed, ease of administration, and lower drug cost, oral hydrochlorothiazide should still be considered as an option for combination diuretic therapy in this patient population.

Key Words thiazide diuretics, heart failure, combination therapy.

(Pharmacotherapy 2014;34(8):882–887) doi: 10.1002/phar.1456

It was estimated that the total cost of managing heart failure in the United States would exceed $34 billion in 2010 and that this figure may triple by 2030.[1] Heart failure affects upward of 5.7 million Americans and is responsible for nearly 1 million hospitalizations each year.[2] Hospitalization is typically driven by worsening of heart failure symptoms and fluid overload. The American College of Cardiology and the American Heart Association, as well as the Heart

Failure Society of America, recommend that patients hospitalized for heart failure who have evidence of fluid overload receive intravenous loop diuretics.[3, 4]

Despite optimization of intravenous loop diuretic therapy, some patients may still have persistent volume overload and be termed diuretic resistant.[5] Hypertrophy of the cells of the distal convoluted tubule and a resultant increase in sodium reabsorption may contribute to the development of this state.[6] By administering a thiazide diuretic, it is possible to overcome the compensatory change and restore diuresis.[5] For patients who do not respond to initial treatment with loop diuretics alone, current guidelines recommend adding a second type of diuretic, specifically a thiazide or spironolactone.[3, 4]

Data regarding the addition of thiazide diuretics to augment diuresis in patients with heart failure and loop diuretic resistance are limited. Metolazone has been the most commonly studied; however; consistent benefits across a number of thiazide agents suggests a "class effect."[5] Despite inclusion in guideline recommendations, only oral, and not intravenous, chlorothiazide (CTZ) has been investigated in this population.[7] Oral hydrochlorothiazide (HCTZ) was studied independently and was shown to be effective in enhancing diuresis in this population.[8] In an economic context alone, oral HCTZ compares favorably to intravenous CTZ, as HCTZ is available at an average wholesale price of just $0.13–0.18/dose as opposed to $519.62 for CTZ.[9] Given the lack of comparative data, ease of oral administration, and lower cost associated with HCTZ compared with intravenous CTZ, this study was conducted to compare the diuretic effects of oral HCTZ and intravenous CTZ among patients hospitalized with heart failure who were already receiving loop diuretic therapy.

Methods

This retrospective review was approved by the institutional review board and encompassed all inpatients at The Ohio State University's Wexner Medical Center within the Richard M. Ross Heart Hospital (Columbus, OH) admitted between September 1, 2009, and August 31, 2011. Patients with a simultaneous active order for both intravenous furosemide and either oral HCTZ or intravenous CTZ were initially identified by using historical medication billing and dispensing data. To be included, patients were required to be treated with intravenous furosemide, administered by continuous infusion or intermittent bolus dosing, at a total daily dose of 160 mg or greater for a period of at least 48 hours (24 hrs before and after thiazide diuretic). While maintained on a consistent intravenous furosemide dose, patients must have also been administered at least one dose of either HCTZ or CTZ. Administration of all ordered medications was confirmed through provider documentation in the electronic medication administration record. Recorded urine output must have been available for a minimum of 24 hours before and after the initial dose of either thiazide diuretic. Selection of thiazide agent was at the discretion of the prescriber; no guiding institutional protocol was in place at the time of this study. Common practice at the institution during the time of the study was to restrict fluid intake of patients with heart failure to a maximum of 2000 ml/day. Doses of intravenous CTZ were prepared in a volume of 100 ml.

Patients aged 18–89 years with a diagnosis of heart failure were screened. Exclusion criteria were prehospitalization use of a thiazide or thiazide-type diuretic and receipt of any of the following interventions during hospitalization, before or within 24 hours after the first administration of HCTZ or CTZ: alternative diuretics other than the aldosterone antagonists (e.g., bumetanide, torsemide, metolazone, ethacrynic acid, acetazolamide, amiloride, or triamterene), vasopressin receptor antagonists (conivaptan, tolvaptan), intermittent hemodialysis, continuous renal replacement therapy, or ultrafiltration.

The primary outcome was change in 24-hour urine output after the initial dose of either thiazide diuretic. Secondary outcomes included change in weight loss and occurrence of adverse events including hypokalemia (potassium level < 4 mEq/L), hypomagnesemia (magnesium level < 2 mEq/L), and change in serum creatinine concentration. Other data collected included baseline characteristics, hospital length of stay, in-hospital mortality, and institutional 30-day readmission rate.

Presented as a poster at the 17th Annual Scientific Assembly of the Heart Failure Society of America, Orlando, Florida, September 23, 2013.

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Statistical Analysis

Continuous variables were evaluated by using a Student *t* test or Wilcoxon rank sum test as appropriate. Categorical variables were evaluated by using a χ^2 test or Fisher exact test as appropriate. A post hoc multivariable regression model was built by using linear regression methods. Input variables were chosen according to clinical suspicion. Values are expressed as median (interquartile range [IQR]) for continuous variables and as number (percentage of the group from which they were derived) for categorical variables. A p value less than 0.05 was considered to indicate a statistically significant difference. Statistical analyses were performed by using IBM SPSS Statistics, version 19 (IBM, Somers, NY).

Results

A total of 329 subjects were identified for review: 245 in the oral HCTZ group and 84 in the intravenous CTZ group. After application of the inclusion and exclusion criteria, the final analysis included 28 patients in the oral HCTZ group and 54 patients in the intravenous CTZ group (Table 1).

Baseline demographics were similar between the two groups with the exception of a significantly greater percentage of women in the HCTZ group (50% vs 22.2%, p=0.01) (Table 2). At admission, both groups were receiving comparable regimens of evidenced-based therapies for heart failure. Although a similar percentage of patients were taking oral loop diuretics before hospitalization, the median daily dose was greater in the HCTZ group (p=0.03).

Before the addition of thiazide diuretic administration, medical therapy was comparable in each group (Table 3). Continuous furosemide infusions were used in 65 patients (79.3%), with no significant difference between groups. The median intravenous furosemide daily dose received during the study period was 240 mg in both groups. With regard to thiazide diuretic dosing, the HCTZ group received a total median [IQR] dose of 25 mg [25–50 mg], and the CTZ group received 500 mg [250–750 mg] (based on 1:10 relative potency of HCTZ:CTZ for the comparison, p<0.01).[10]

Mean 24-hour urine output preceding the administration of either thiazide diuretic was similar between groups (p=0.28, Table 4). After the addition of each thiazide agent, mean 24-hour urine output increased in both groups. However, mean change in 24-hour urine output was significantly greater with intravenous CTZ compared with oral HCTZ (p=0.005). No significant differences in secondary end points, including change in weight loss, serum creatinine concentration, or electrolyte disturbances, were identified.

A post hoc multivariable analysis was performed. Patients receiving CTZ had a mean 696.6-ml (95% confidence interval [CI] 22.98–1370.3 ml, p=0.04) greater increase in urine output than did patients treated with HCTZ after adjusting for sex (male patients 688.1 ml, 95% CI −21.6 to 1397.81 ml, p=0.06) and those with a baseline serum creatinine concentration ≤ 2 (615.7 ml, 95% CI −20.7 to 1252.1 ml, p=0.06).

Table 1. Inclusion and Exclusion Criteria Used in the Patient Selection Process

Criteria	Oral HCTZ Group	Intravenous CTZ Group
Inclusion criteria		
Treated with oral HCTZ or intravenous CTZ in addition to intravenous furosemide	245	84
Received intravenous furosemide by continuous infusion or intermittent bolus at a consistent dose ≥ 160 mg/day for 24 hrs before and after thiazide diuretic	59 (24.1%)	73 (86.9%)
Exclusion criteria		
Thiazide administration not documented	2 (3.4%)	2 (2.7%)
Thiazide or thiazide-type diuretic used before admission	9 (15.3%)	9 (12.3%)
In-hospital use of alternative diuretic (e.g., bumetanide, torsemide, metolazone, ethacrynic acid, acetazolamide, amiloride, or triamterene)	18 (30.5%)	0 (0%)
Received IHD, CRRT, or UF	2 (3.4%)	7 (9.6%)
Incomplete urine output data	0 (0%)	1 (1.4%)
Total no. of included patients	28	54

CTZ = chlorothiazide; HCTZ = hydrochlorothiazide; IHD = intermittent hemodialysis; CRRT = continuous renal replacement therapy; UF = ultrafiltration.
Data are no. of patients or no. (%) of patients.

Table 2. Demographic and Clinical Characteristics of the Study Patients

Characteristic	Oral HCTZ Group (n=28)	Intravenous CTZ Group (n=54)	p Value
Age (yrs)	64 [47–73]	63.5 [51–71]	0.97
Female	14 (50%)	12 (22.2%)	0.01
Race-ethnicity			
Caucasian	22 (78.6%)	41 (75.9%)	0.92
African American	5 (17.9%)	10 (18.5%)	
Other	1 (3.6%)	3 (5.6%)	
Admission weight (kg)	96 [81–105]	97 [76–117]	0.5
Serum creatinine concentration (mg/dl)	1.6 [1.0–2.3]	1.7 [1.2–2.7]	0.26
Blood urea nitrogen (mg/dl)	39.5 [21–58]	34 [16–52]	0.49
Serum sodium (mEq/L)	135 [133–139]	137 [132–139]	0.95
Brain natriuretic peptide (pg/ml)	1008 [603–1465]	899 [642–1490]	0.91
LVEF ≤ 40%	21 (75%)	40 (74.1%)	0.99
LVEF (%) for patients with LVEF ≤ 40%	25 [20–40]	20 [15–30]	0.18
Ischemic origin	12 (42.9%)	27 (50%)	0.54
NYHA functional class			
III	17 (60.7%)	35 (64.8%)	0.81
IV	11 (39.3%)	19 (35.2%)	
Medications at admission			
Aldosterone antagonist	7 (25%)	18 (33%)	0.61
ACE inhibitor/ARB	13 (46.4%)	24 (44.4%)	0.82
β-Blocker	20 (71.4%)	42 (77.8%)	0.78
Digoxin	6 (21.4%)	11 (20.4%)	0.99
Hydralazine/nitrate	7 (25%)	11 (20.4%)	0.78
Treated with loop diuretic before admission	26 (92.9%)	49 (90.7%)	0.66
Oral daily loop diuretic dose before admission in furosemide equivalents (mg/day)[a]	160 [80–320]	120 [40–160]	0.03
Length of hospital stay (days)	16 [9–27]	16 [11–24]	0.78
In-hospital mortality	1 (3.6%)	6 (11.1%)	0.41
Institutional readmission within 30 days of discharge	6/27 (22.2%)	13/48 (27.1%)	0.53

HCTZ = hydrochlorothiazide; CTZ = chlorothiazide; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.
Data are median [interquartile range] or no. (%) of patients.
[a]Oral loop diuretic equivalents: furosemide 40 mg = torsemide 20 mg = bumetanide 1 mg.[4]

Nonsignificant factors removed from the final model included age, inotrope use, and adjusted equivalent dose of thiazide agent.

Discussion

Patients with heart failure and volume overload who develop loop diuretic resistance present a therapeutic challenge. The addition of a thiazide diuretic to background intravenous loop diuretics, also known as combination diuretic therapy, has been shown to augment diuresis by establishing sequential nephron blockade. One study investigated the effect of adding oral chlorothiazide 500 mg/day to the regimens of 32 hospitalized patients already receiving furosemide 160–320 mg/day.[7] This intervention led to significantly improved in-hospital weight loss (mean 4.8 kg) without an associated increase in serum creatinine concentration. However, weight loss may be subject to a number of confounders, and urine output was not reported. Another study reported an experience with the addition of oral hydrochlorothiazide 25–100 mg/day in 20 hospitalized patients receiving high-dose furosemide (250–4000 mg/day).[8] After treatment, diuresis improved significantly, with a mean daily urine output increase greater than 1 L. The authors also reported a mean total weight loss of 6.7 kg over the course of treatment. Numerous analyses have detailed the effect of adding a variety of thiazide and thiazide-type diuretics to heart failure patients with loop diuretic resistance. These investigations have consistently demonstrated evidence of enhanced diuresis, using outcomes such as urine output, weight loss, and urinary sodium concentration.[5] However, these data are frequently limited by small samples sizes and lack of a control group.

Historically, metolazone has been the most frequently investigated intervention, and although it is another cost-effective oral option for combination diuretic therapy, concerns exist with its prolonged half-life and potential for metabolic derangements including persistent

Table 3. Characteristics of In-Hospital Treatment

Characteristic	Oral HCTZ Group (n=28)	Intravenous CTZ Group (n=54)	p Value
Concurrent inotrope use			
Dobutamine	10 (35.7%)	21 (38.9%)	0.97
Milrinone	6 (21.4%)	14 (25.9%)	
Dobutamine and milrinone	3 (10.7%)	7 (13%)	
Dopamine	0 (0%)	0 (0%)	
Concurrent nesiritide use	1 (3.6%)	1 (1.9%)	0.99
Total daily dose of intravenous furosemide (mg)	240 [160–360]	240 [240–360]	0.06
Administered by continuous infusion	21 (75%)	44 (81.5%)	0.57
Thiazide diuretic dosing[a]			
24-hr oral HCTZ dose (mg)	25 [25–50]		< 0.01
Dose range (mg)	12.5–100		
No. of doses received	1.4 (mean), 1 (median)		
24-hr intravenous CTZ dose (mg)		500 [250–750]	
Dose range (mg)		250–2000	
No. of doses received		1.6 (mean), 2 (median)	

CTZ = chlorothiazide; HCTZ = hydrochlorothiazide.
Data are no. (%) of patients or median [interquartile range].
[a]Comparison assumes 10:1 relative potency of CTZ:HCTZ.[10]

Table 4. Primary and Secondary Outcomes

Outcome	Oral HCTZ Group (n=28)	Intravenous CTZ Group (n=54)	p Value
Urine output 24 hrs before thiazide diuretic administration (ml)			
Mean ± SD	2104 ± 830	2342 ± 978	0.28
Median [IQR]	1990 [1350–2960]	2350 [1650–2875]	
Urine output 24 hrs after thiazide diuretic administration (ml)			
Mean ± SD	3038 ± 917	4128 ± 1755	0.003
Median [IQR]	3038 [2600–3750]	4213 [2975–5425]	
Change in 24-hr urine output (ml)			
Mean ± SD	934 ± 943	1786 ± 1737	0.005
Median [IQR]	978 [−50 to 1711]	1625 [350 to 2982]	
Change in 24-hr weight loss (kg)	0.15 [−0.4 to 1.4]	0.8 [−0.4 to 2.9]	0.14
Change in S_{cr} 24 hrs after thiazide diuretic administration (mg/dl)	0.04 [−0.04 to 0.09]	0.06 [−0.07 to 0.16]	0.65
Increase in $S_{cr} \geq 0.3$ mg/dl	1 (3.6%)	5 (9.3%)	0.66
Electrolyte disturbances within 24 hrs after thiazide diuretic administration			
Hypokalemia (potassium level < 4.0 mEq/L)	20 (71.4%)	45 (83.3%)	0.21
Hypomagnesemia (magnesium level < 2.0 mEq/L)	5 (17.9%)	9 (16.7%)	0.84

CTZ = chlorothiazide; HCTZ = hydrochlorothiazide, S_{cr} = serum creatinine concentration.
Data are mean ± SD, median [interquartile range], or no. (%) of patients.

hypokalemia and contraction alkalosis.[4, 11] Prior to the current study, despite its recommendation in national guidelines, there had been no published investigation of intravenous CTZ when added to standard intravenous furosemide to augment diuresis in hospitalized patients with heart failure. Given the rising costs of heart failure management and greater expense of intravenous CTZ, our study was undertaken to compare the response of intravenous CTZ with that of oral HCTZ.

In our study, both oral HCTZ and intravenous CTZ enhanced diuresis within the targeted population. However, compared with HCTZ, patients receiving CTZ demonstrated a significantly greater increase in 24-hour urine output after initiation, as well as a trend toward greater improvement in 24-hour weight loss, our surrogate marker for fluid balance. As a possible contributor, doses of CTZ were significantly higher than those for HCTZ even after accounting for the 10-fold relative difference in potency between agents.[10] Although thiazide agent dose was not determined to be a predictor of response in our analysis, this could be due to a lack of power given the limited sample size. Additional analysis suggested the possibility of a dose-response relationship, as total 24-hour HCTZ doses ≥ 50 mg and CTZ doses ≥ 500 mg were more likely to enhance urine output (an increase > 500 ml over 24 hrs) vs lower doses: 7 (100%) of 7 patients vs 12 (57%) of 21

patients for HCTZ and 28 (85%) of 33 patients vs 12 (57%)of 21 patients for CTZ.

With regard to adverse events, like prior investigations, hypokalemia was observed frequently in both groups.[7, 8] Our definition of hypokalemia, < 4.0 mEq/L, may have inflated its occurrence; however; at our institution values below this threshold trigger protocol-driven potassium replacement. These data further support the need for frequent chemistry evaluations regardless of the agent chosen for combination diuretic therapy. Previously, studies have reported variable effects of combination diuretic therapy on renal function.[5] No significant variation in serum creatinine concentration was observed; however, the 24-hour period after thiazide administration included in our analysis may have not allowed for detection.

Although a detailed pharmacoecomonic analysis was not planned for this study, at the doses administered, the relative cost of CTZ treatment was more than 2000-fold greater than HCTZ over the observed period.

As with prior analyses on this subject matter, this study carries limitations. Although most patient characteristics were similar at baseline, this report is inherently limited by its retrospective design and lack of randomization. Our study included only inpatients with New York Heart Association functional class III or IV heart failure, and although not significantly different between groups, many patients were not receiving all evidence-based heart failure medications during the study period. Although this investigation includes more patients than previously published documents, the limited numbers of patients may still have impaired our ability to identify differences in baseline characteristics and secondary outcome parameters. Despite capturing recorded objective measures of response, including urine output and weight loss, it was not possible to assess subjective measures of clinical status, such as dyspnea, that may dictate treatment course. The 24-hour follow-up duration served to minimize the influence of confounding factors in assessing the impact of HCTZ and CTZ on urine output; however, this also prohibited evaluation of the sustainability of the response.

Conclusion

Among patients hospitalized with heart failure, the addition of either oral HCTZ or intravenous CTZ to a background of intravenous furosemide therapy resulted in enhanced diuresis. The use of CTZ was associated with a more robust initial diuresis compared with HCTZ within the first 24 hours. Given the positive response observed, ease of administration, and lower drug cost, however, oral HCTZ should still be considered as another option for combination diuretic therapy in this patient population. Further prospective analysis, powered to assess clinical outcomes, is required to establish a positive cost-benefit of intravenous CTZ compared with oral HCTZ.

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