ORIGINAL RESEARCH ARTICLE

Cardiovascular Therapeutics

Comparison of Metolazone Versus Chlorothiazide in Acute Decompensated Heart Failure with Diuretic Resistance

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SUMMARY

Aims: Sequential nephron blockade with thiazide-like diuretics is a strategy used to overcome diuretic resistance in acute decompensated heart failure (ADHF), but head-to-head studies are lacking and equipoise exists regarding the preferred thiazide-like diuretic in this setting. We thus compared the effectiveness of oral metolazone versus intravenous (IV) chlorothiazide as add-on therapy to loop diuretics in hospitalized patients with ADHF and renal dysfunction. **Methods:** This retrospective cohort study evaluated the efficacy and safety of oral metolazone versus IV chlorothiazide as add-on therapy to loop diuretics in patients hospitalized with ADHF and renal dysfunction. The primary endpoint was net urine output (UOP) at 72 h after initiation of thiazide-like diuretics. Safety endpoints included worsening renal function, hypotension, and electrolyte abnormalities. **Results:** Fifty-five patients were enrolled with 33 patients receiving metolazone and 22 patients receiving chlorothiazide. There was no difference in median net UOP at 72 h in those receiving metolazone (4828 mL, interquartile range [IQR] 2800–7209 mL) compared to chlorothiazide (3779 mL, IQR 1885–6535 mL) ($P = 0.16$). There was no difference in hypotension, worsening renal function, hyponatremia, or hypokalemia (P = NS for all comparisons). Hospital length of stay was shorter in the metolazone cohort (median 7 days) compared to chlorothiazide (median 15 days), suggesting the chlorothiazide cohort was likely sicker. **Conclusion:** Sequential nephron blockade with either metolazone or chlorothiazide appears to be efficacious and safe in ADHF, renal dysfunction, and diuretic resistance. Given the considerable cost difference favoring oral metolazone, larger randomized studies are warranted to confirm our findings and to exclude the possibility of confounding by indication.

Introduction

Acute decompensated heart failure (ADHF) characterized by volume overload accounts for 90% of the one million heart failure (HF)-related hospitalizations annually in the United States [1]. Data from the Acute Decompensated Heart Failure National Registry (ADHERE) reveal that 88% of patients hospitalized with ADHF receive intravenous (IV) loop diuretics during their admission [1–3]. Despite lacking a proven survival benefit, IV loop diuretics remain a cornerstone of ADHF therapy because of their ability to rapidly relieve congestive symptoms and restore euvolemia. Treatment with loop diuretics are thus recommended as first-line therapy in the treatment of patients with ADHF associated with volume overload [4–6].

In ADHF, volume retention and congestion occurs predominantly due to increased sodium retention by the kidneys, induced by a multitude of upstream mechanisms including neurohormonal activation [4–6]. Loop diuretics exert their therapeutic effect by inhibiting the sodium–potassium–chloride co-transporter in the ascending loop of Henle, a potent site of sodium reabsorption in the nephron. By inhibiting these transporters, loop diuretics provide a means by which excess sodium can be excreted, in turn leading to a potent aquaretic effect as well [7]. However, diuretic resistance may develop in HF patients with prolonged exposure to loop diuretics due to upregulation and hypertrophy of electrolyte transporters in the loop of Henle or distal convoluted tubule [8,9]. When these structural changes occur, the therapeutic effect of loop diuretics is blunted and enhanced sodium and water retention may occur. Diuretic resistance in ADHF becomes particularly challenging in patients with coexisting renal insufficiency as large doses of loop diuretics are often needed to achieve a sufficient threshold to produce even a modest diuretic effect.

Sequential nephron blockade using thiazide-type diuretics has long been proposed as a strategy to overcome diuretic resistance in ADHF by inhibiting sodium reabsorption in the distal

convoluted tubule. Such practice is even supported by the most recent, updated HF guidelines [6,8,9]. Yet, despite the common utilization of this treatment strategy, there are surprisingly few published studies available to guide a standard therapeutic approach. Consequently, the timing and choice of thiazide-type diuretics is often empiric, clinician-dependent, and not sufficiently data driven. Most of the studies and/or case series that do exist are quite small, usually lack comparator groups, and investigated a variety of different, older, and less commonly used thiazide-type diuretics compared to the agents more frequently used today [10–22]. In fact, to the best of our knowledge, not even a single study has been published comparing the effectivenes and safety of two of the most commonly utilized thiazide diuretics in HF, metolazone or chlorothiazide, as add-on therapy to loop diuretics in ADHF. We thus conducted the present pilot study to compare the relative effectiveness of oral metolazone versus IV chlorothiazide as add-on therapy to furosemide in patients hospitalized with ADHF and renal insufficiency.

Methods

This was a single-center, retrospective, cohort study of patients hospitalized with ADHF between June 1, 2008, and December 31, 2011. A cut-off date of June 1, 2008, was chosen as this is when the electronic medical record was first implemented at our institution, which was used to facilitate and ensure the accuracy of the data collection process. The study was approved by the University of Chicago investigational review board (IRB number 12-1403). A detailed review of each patient's electronic medical record was used to obtain and/or confirm patient demographics, comorbid conditions, vital sign information, measurements of total fluid intake and urine output (UOP), home medication records, inpatient medication administration records, echocardiogram reports, and laboratory values. Individual, daily physician and nursing notes as well as all international classification of disease, ninth edition (ICD-9) codes were also reviewed to verify the accuracy of the data.

Patient Selection

To be included into this study, patients were required to meet the following entry criteria:

1. ≥18 years of age.
2. Admitted to the hospital with a diagnosis of ADHF (preserved or reduced ejection fraction [EF]) based on the ICD-9 codes.
3. Presence of significant renal insufficiency defined by a creatinine clearance of 15–50 mL/min as calculated on day one of the study period (i.e., the day when either metolazone or chlorothiazide was added to the medical regimen). Creatinine clearance was calculated using the Cockcroft-Gault equation based on ideal body weight [23].
4. Initial diuretic treatment was with IV furosemide monotherapy.
5. Metolazone or chlorothiazide therapy was subsequently added to furosemide during the ADHF hospitalization with maintenance of this combined regimen for at least 72 h in duration. A minimum of 72 h of exposure to add-on thiazide-type diuretic therapy was chosen to ensure sufficient time for the full effects of both metolazone and chlorothiazide to occur and for sufficient exposure to each drug to allow for a meaningful comparison.

Day one of the study period was the date on which add-on therapy with metolazone or chlorothiazide was initiated. All patients received the final dose of metolazone a minimum of 48 h after its initiation, and for chlorothiazide, the final dose was administered at a minimum of 60 h after its initiation. These specific criteria were chosen based on established drug half-lives and recommended dosing intervals; metolazone has a half-life of approximately 20 h, allowing for once-daily dosing as compared to IV chlorothiazide which has a shorter half-life and is thus often dosed twice daily [24,25].

Patients were excluded from the study for any of the following reasons:

1. If a patient received both metolazone and chlorothiazide during the study period.
2. If a patient received a thiazide or thiazide-like diuretic in the hospital prior to the study period.
3. The presence of end-stage renal disease requiring dialysis.
4. Use of any form of renal replacement therapy (i.e., continuous veno-venous hemofiltration and/or slow, continuous ultrafiltration) during the index hospital stay prior to being treated with either metolazone or chlorothiazide (patients who may have ultimately progressed to requiring renal replacement therapy after the study period were not excluded).
5. The presence of cirrhosis.
6. Severe malnutrition as defined by an albumin of <2.5 g/dL.

Study Endpoints

The primary efficacy endpoint in this study was net UOP (total recorded UOP minus total recorded fluid intake) 72 h after the addition of either oral metolazone or IV chlorothiazide therapy to the patient's furosemide regimen. Secondary efficacy endpoints included total UOP at 72 h, net and total UOP at 12-h increments after initiation of metolazone or chlorothiazide, respectively, and achievement of at least 3000 mL of net UOP at 72 h.

Safety endpoints included worsening renal function (defined by an increase in serum creatinine of >0.5 mg/dL from the patients' baseline value on the day of thiazide-type diuretic initiation); worsening electrolyte imbalances during the study period including hypokalemia (defined by a potassium value of <3.5 mEq/L), hypomagnesemia (defined by a magnesium value of <1.6 mg/dL), and hyponatremia (defined by a sodium value of <135 mEq/L); and hypotension (measured systolic blood pressure <90 mmHg and/or a 20% decrease in systolic blood pressure from baseline at any point during the study period).

Statistical Methods

Baseline characteristics for all patients were expressed as percentages for categorical variables and mean ± standard deviation for continuous variables that were normally distributed. Right-skewed data were presented as median and interquartile range (IQR). Differences between treatment groups for categorical

variables were analyzed using the chi-square or Fisher exact test. Continuous variables were analyzed using the Student *t*-test or Wilcoxon–Mann–Whitney test, as determined by the normality of the data. All statistical analyses were performed using Stata version 11.0, College Station, TX, USA.

We initially identified 292 patients with ADHF who received IV furosemide plus oral metolazone or IV chlorothiazide during the study period. After applying the strict inclusion and exclusion criteria, we arrived at a final study cohort of 55 patients (33 patients in the oral metolazone group and 22 patients in the IV chlorothiazide group). Figure 1 displays a flow chart of where the major exclusion criteria were applied.

Results

Baseline Characteristics

Baseline demographics were similar for each of the two treatment groups (Table 1). The median age of the patients was 70 years (IQR 59–76.5 years), 68% were male, and the majority (78.6%) were African American. There were no major differences in comorbidities between the two cohorts (Table 1). This was largely a reduced EF HF population with a median EF 33% (IQR 18.8–49.5%). In fact, only two patients (one from each cohort) had an EF of 50% or greater. Baseline home HF medication regimens were similar in both groups, although patients in the metolazone group were prescribed a slightly higher home loop diuretic dose equivalent as compared to the chlorothiazide group (90 mg vs. 70 mg; $P = 0.01$) (Table 1). Interestingly, significantly more patients in the metolazone arm (n = 7) compared to the chlorothiazide arm (n = 0) were being treated with device therapy (biventricular pacemakers and/or implantable cardiac defibrillators) ($P = 0.02$).

Diuretic Dosing

There were some notable differences in total diuretic dosing between the groups during the study period. Over the course of the 72-h study period, the median total dose of IV furosemide was 500 mg (IQR 240–720 mg) in the metolazone group and 1015 mg (IQR 775–1300 mg) in the chlorothiazide group ($P < 0.001$). The median metolazone total dose was 7.5 mg (IQR 7.5–10 mg), and the median chlorothiazide total dose was 2500 mg (IQR 1750–2500 mg). When diuretic dosing was analyzed by each individual day of the 72-h study period, the median daily dose of metolazone was 2.5 mg (IQR 2.5–2.5 mg). The median daily dose of chlorothiazide was 500 mg (IQR 500–875 mg) on day 1, 750 mg (IQR 500–1000 mg) on day 2, and 1000 mg (625–1000 mg) on day 3.

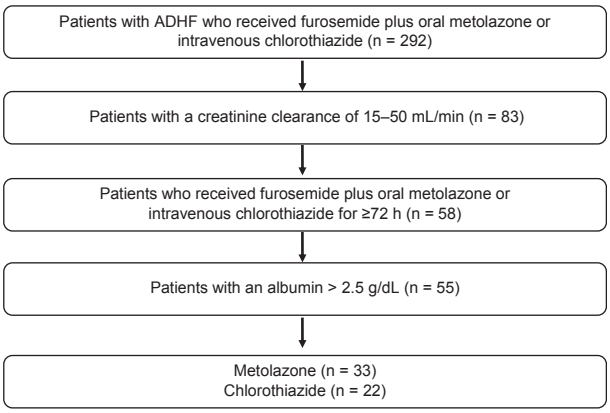

Figure 1 Flow chart depicting the application of the inclusion and exclusion criteria to arrive at our final study cohort of 55 patients. Specifically, there were 33 patients who received metolazone plus furosemide and 22 patients who received chlorothiazide plus furosemide.

Efficacy Endpoints

Although numerical trends were observed favoring metolazone, there were no statistically significant differences among the two cohorts for any of the efficacy endpoints. For the primary endpoint of net UOP at 72 h, the metolazone group had a median net UOP of 4828 mL (IQR 2800–7209 mL) versus a median 3779 mL (IQR 1885–6535 mL) with chlorothiazide ($P = 0.16$) (Figure 2). The secondary endpoint of net UOP of at least 3000 mL achieved at 72 h occurred in 73% of patients receiving metolazone versus 55% of patients treated with chlorothiazide ($P = 0.17$). A breakdown of net UOP at each 12-h interval in the study between the two groups can be seen in Figure 3. Finally, there was no difference in total UOP between metolazone (median 9442 mL, IQR 5943–12441) versus chlorothiazide (median 7500 mL, IQR 5800–10002 mL) ($P = 0.47$).

Safety Endpoints

There were no significant differences between the metolazone group and the chlorothiazide group in regard to the defined safety endpoints. Overall, only two patients in the metolazone group and three patients in the chlorothiazide group experienced worsening renal function and hypotension occurred rarely in either group. Significant hypokalemia, however, was quite common, occurring in nearly half of the patients from both groups.

Subgroup Analyses

In those patients with the most impaired renal function (restricted to those with a creatinine clearance of 15–30 mL/min), there was no significant difference in net UOP at 72 h between the metolazone group (n = 21; median net UOP of 4696 mL, IQR 2872–6858) and the chlorothiazide group (n = 14; median net UOP 3240, IQR 2218–6675) ($P = 0.44$, Figure 4). However, when we extended the analyses to those with a creatinine clearance of 15–40 mL/min, there was a trend toward greater net UOP at 72 h favoring metolazone-treated patients (n = 28; median net UOP of 4762 mL, IQR 2955–6895 mL) compared to chlorothiazide-treated patients (n = 20; median net UOP 3239 mL, IQR 982–5727 mL) ($P = 0.11$). Net UOP of at least 3000 mL at 72 h also trended in favor of metolazone-treated patients (75% vs. 50% achieved; $P = 0.07$).

In terms of acuity/severity of illness, the use of inotropic therapy during the hospitalization was similar between the metolazone group (six patients on dobutamine, one patient on milrinone) and the chlorothiazide group (seven patients on dobutamine, one patient on dobutamine plus dopamine) ($P = 0.22$). However,

Table 1 Patient baseline demographics and clinical characteristics

Baseline data	Metolazone (n = 33)	Chlorothiazide (n = 22)	*P*-value
Age—years (IQR)	69 (60–78)	70.5 (58–76)	0.84
Female—No. (%)	22 (67)	15 (68)	0.91
Ethnicity—No. (%)			
African American	28 (85)	16 (73)	0.26
Caucasian	5 (15)	6 (27)	
Weight—kg (IQR)	71.5 (62–81.5)	69.6 (61.0–81.8)	0.75
EF—% (IQR)	35 (17–56)	31 (21–38)	0.79
HFpEF—No. (%)	10 (30)	7 (32)	0.91
HFrEF—No. (%)	23 (70)	15 (68)	0.91
Atrial fibrillation or atrial flutter	11 (33)	8 (36)	0.82
Ventricular tachycardia or ventricular fibrillation	0 (0)	2 (9)	0.08
Valvular disease	7 (21)	5 (23)	0.89
Chronic kidney disease	29 (88)	17 (77)	0.30
Diabetes mellitus	21 (64)	11 (50)	0.32
Hyperlipidemia	10 (30)	5 (23)	0.54
Hypertension	22 (67)	13 (59)	0.57
Coronary artery disease	17 (52)	10 (45)	0.66
Acute coronary syndrome	8 (24)	8 (36)	0.90
Implantable cardioverter defibrillator	6 (18)	1 (5)	0.14
Bi-ventricular pacemaker	7 (21)	0 (0)	0.02
Scr—mg/dL (IQR)	2.2 (1.8–2.9)	2.2 (2.0–2.8)	0.88
CrCl—mL/min (IQR)	27.5 (22.6–36.2)	26.1 (22.1–36.2)	0.71
CrCl 15–30 No. (%)	21 (64)	14 (64)	
CrCl 31–40 No. (%)	7 (21)	6 (27)	
CrCl 41–50 No. (%)	5 (15)	2 (9)	
Baseline UOP—mL* (IQR)	1600 (850–2100)	817.5 (460–2790)	0.31
Median furosemide dose before adding thiazide-type diuretic (mg)*	100 (40–320)	150 (0–280)	0.53
Home mediations			
Loop diuretics			
Furosemide	24 (73)	15 (68)	0.09
Torsemide	5 (15)	1/(5)	
Bumetanide	3 (9)	1 (5)	
None	1 (3)	5 (23)	
Furosemide dose equivalent (mg) (median, IQR)	90 (80–160)	70 (40–80)	<0.01
Other diuretics			
Thiazide	13 (39)	5 (23)	0.12
Thiazide-type	0 (0)	2 (9)	
Aldosterone antagonist	5 (15)	2 (9)	
Angiotensin converting enzyme inhibitor	13 (39)	13 (59)	0.35
Angiotensin receptor blocker	5 (15)	6 (27)	0.77
Beta blocker	23 (70)	14 (64)	0.64
Digoxin	3 (9)	2 (9)	0.99
Hydralazine	12 (36)	8 (36)	0.99
Nitrates	13 (39)	6 (27)	0.90

CrCl, creatinine clearance; EF, ejection fraction; IQR, interquartile range; IV, intravenous; HFpEF, heart failure with a preserved ejection fraction; HFrEF, heart failure with a reduced ejection fraction; kg, kilograms; mg, milligrams; No, number; SCr, serum creatinine; UOP, urine output. *24 h prior to add-on diuretic therapy.

median hospital length of stay was substantially shorter in the metolazone group (7 days, IQR 5–12 days) compared to the chlorothiazide group (16 days, IQR 11–21 days) ($P = 0.03$).

Discussion

The management of diuretic resistance in patients hospitalized with ADHF remains a complex, difficult to treat condition with widely varying and often empiric strategies. The addition of thiazide-type diuretics to loop diuretics is hampered by a relative paucity of supportive, published data, especially in the setting of renal dysfunction. Additionally, whether metolazone or chlorothiazide, the two most commonly used thiazide-type diuretics in HF, is of superior efficacy and/or safety has not been studied. In fact, to our knowledge, this is the first study (prospective or retrospective) to compare the effects of metolazone versus chlorothiazide as add-on

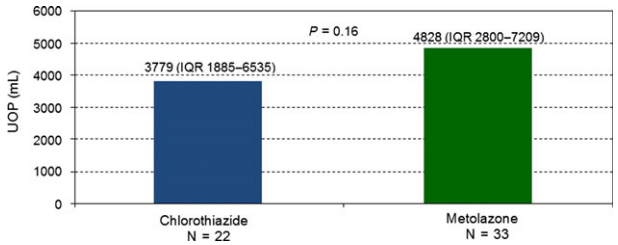

Figure 2 Despite a trend favoring metolazone, there was no significant difference in the primary efficacy endpoint of net urine output (UOP) at 72 h among the two cohorts.

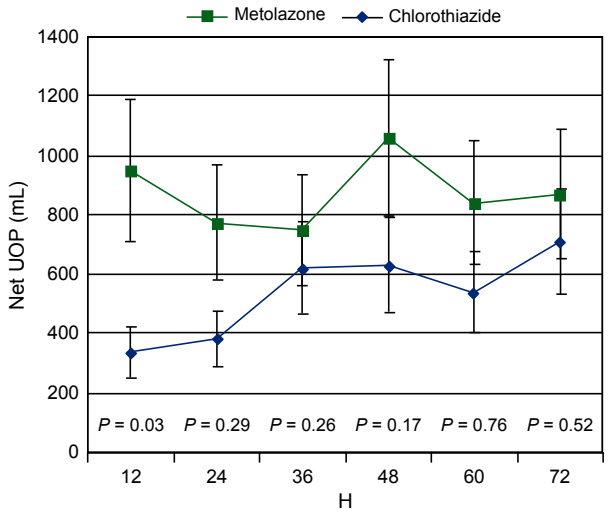

Figure 3 Net urine output (UOP) was derived from each 12-h interval spanning the entire 72-h study period during which add-on diuretic therapy was utilized. Net UOP was calculated as total collected UOP—total documented fluid intake. As with the primary endpoint of net UOP at 72 h, while the metolazone group had numerically greater net UOP at each 12-h increment compared to chlorothiazide, this did not meet statistical significance with the exception of the first 12 h of therapy.

therapy in patients hospitalized with ADHF. We demonstrate that the addition of thiazide-type diuretics does, indeed, effectively augment diuresis in ADHF patients with diuretic resistance, even in the face of significant renal dysfunction. Perhaps as importantly, we also did not observe a statistically significant difference between oral metolazone and IV chlorothiazide in terms of either efficacy or safety of augmenting diuresis in this challenging clinical setting.

Hospitalizations for ADHF have become a topic of growing national attention in both the research and political arenas because of its increasing frequency and burden on healthcare resources. In addition to survival, endpoints of relevance include identifying ways to reduce both hospital length of stay and readmissions. Considerable evidence exists correlating the degree of achieved volume removed during ADHF hospitalizations with improved ADHF outcomes, including reduced hospital readmissions [26–33]. Thus, there has long been substantial interest to identify superior strategies to effectively and safely remove volume in ADHF. For instance, because of concerns related to potential adverse effects of diuretics on renal function coupled with encouraging results from the Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) trial, the Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome (CARRESS-HF) trial was recently conducted to compare an aggressive diuretic strategy versus ultrafiltration in ADHF and renal insufficiency [27,34]. Unfortunately, the strategy of ultrafiltration was not superior and, perhaps somewhat surprisingly, was associated with an increase in adverse events, particularly worsening renal function [34].

At around the same time as CARRESS-HF, [35] the large, multicenter trial of Diuretic Optimization Strategies Evaluation (DOSE) study comparing a continuous infusion of furosemide compared to IV boluses of furosemide was performed. Ultimately, this study failed to identify a benefit favoring either diuretic strategy [36]. While data now exist comparing ultrafiltration versus diuretics and continuous versus bolus loop diuretic treatment in ADHF, surprisingly few data exist regarding the common practice of

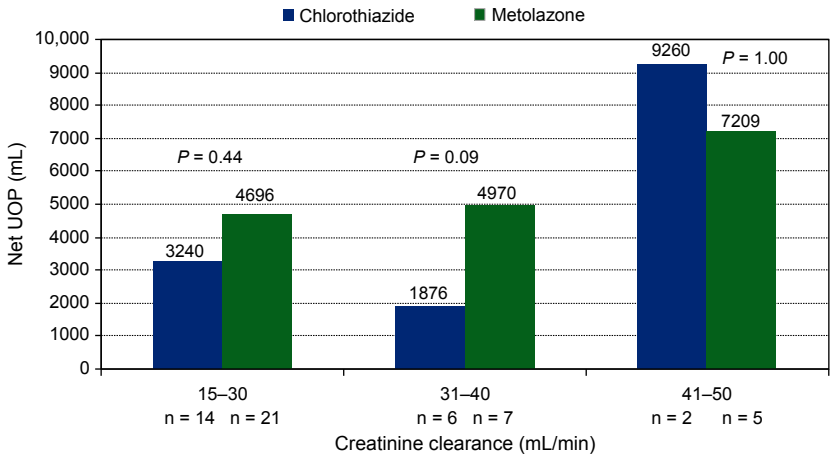

Figure 4 A subgroup analysis of net urine output (UOP) during the 72-h study period according to creatinine clearance revealed no significant difference between the two cohorts.

add-on therapy with thiazide-type diuretics in ADHF, particularly in patients with coexisting renal insufficiency who are among the highest risk for HF morbidity and mortality [37–40]. Whereas previous small, retrospective studies have assessed the *individual* efficacy of either metolazone or chlorothiazide in ADHF, a head-to-head comparison has not been performed to date [10,12,16,19–22]. Furthermore, there exist no published studies assessing the relative effectiveness and safety of thiazide-type diuretics in the setting of ADHF and renal insufficiency, a challenging but not particularly uncommon clinical scenario in ADHF when loop diuretic augmentation is needed due to diuretic resistance.

As clinical equipoise exists regarding the efficacy and safety of individual thiazide-type diuretics frequently used in HF, other factors may dictate the selection of drug for an individual patient. For instance, chlorothiazide has the advantage of being available in IV form, which may be advantageous in those with significant gastrointestinal edema and variable absorption or in patients who cannot take oral medications. On the other hand, there is concern that chlorothiazide may not be adequately filtered through the glomerulus to reach its site of action in patients with renal insufficiency [10,24,41]. Metolazone is thought to not be significantly affected by impaired glomerular filtration but may suffer from reduced bioavailability in patients with significant gastrointestinal edema [10,25,41]. Importantly, however, where equipoise does not exist among these thiazide diuretics is in regard to cost. Perhaps underappreciated is that a standard 250 or 500 mg dose of IV chlorothiazide is considerably more expensive than a 2.5 or 5.0 mg dose of PO metolazone. In fact, a single IV dose of chlorothiazide 500 mg (~$348.00) is on average more than 200-fold more expensive than a single PO dose of metolazone 5 mg (~$1.51) [42,43]. Because the inpatient management of HF is currently the single most expensive diagnosis-related group (DRG), with an estimated annual cost of 20 million dollars, identifying cost-saving measures without compromising patient care is of critical importance [44]. Although the current study should best be considered hypothesis-generating given the epidemiologic limitations of retrospective studies, should a subsequent larger, prospective study demonstrate noninferiority of PO metolazone compared to IV chlorothiazide, the potential cost-savings would be of significant value.

While not achieving statistical significance in this study, there were numerical trends in the measured efficacy endpoints that favored metolazone. Specifically, patients receiving metolazone achieved a greater net UOP at 72 h than those receiving chlorothiazide and a greater percentage of patients in the metolazone group achieved at least 3000 mL of net UOP in 72 h. Moreover, it appears that trends favoring metolazone occurred despite the fact that chlorothiazide may have actually been dosed more aggressively than metolazone. According to current HF guidelines, it is recommended to begin with doses of chlorothiazide 250 mg and metolazone 2.5 mg, respectively, and up titrate as needed [5,6]. Yet, in this study, the median total amount of add-on thiazide-type diuretic received in the 72-h study period was 2500 mg of chlorothiazide and 7.5 mg of metolazone. Based on this approximate conversion, patients in the chlorothiazide group received about three times more thiazide diuretic than metolazone-treated patients.

The aforementioned numerical trends should be interpreted with caution and should best be considered exploratory as there are several reasons to believe that patients in the chlorothiazide cohort may have been sicker or at least more diuretic resistant. First, although the baseline home doses of loop diuretic prior to admission were similar between the two groups, in the chlorothiazide treatment group, the total IV furosemide dose was 1.5 times greater prior to the initiation of chlorothiazide and twice as great during the 72-h study period as compared to the total IV furosemide dose in the metolazone group during the same, corresponding time periods (Table 1). Next and perhaps most suggestive of a difference in ADHF severity between the two groups is the significantly longer hospital length of stay in the chlorothiazide group (median 16 days) compared to the metolazone group (median 7 days). Finally, it is possible that some patients who received IV chlorothiazide (and not PO metolazone) did so because of a perceived inability to take oral medications, a likely sign of increased severity of illness.

From a safety perspective, neither hypotension nor worsening renal function was common in either thiazide cohort. Not unexpectedly, a substantial percentage of patients from both groups developed hypokalemia or hyponatremia during treatment, indirectly underscoring the potency of this class of medications, particularly when combined with a loop diuretic.

Study Limitations

There are several important limitations of this study. First, this was a single-center, retrospective, non-randomized study and is thus subject to the biases and confounders inherent to such studies. As such, while this pilot study comparing IV chlorothiazide and PO metolazone may be informative, the findings should be considered hypothesis-generating only. Second, although UOP results were meticulously gathered for each patient via the electronic medical record, the possibility of information bias could exist should significant errors in UOP charting have occurred. However, both cohorts in the study would be equally at risk for any errors that may have occurred in the recording of UOP. Additionally, the size of the study was relatively small. However, we felt this was ultimately necessary to apply relatively strict inclusion and exclusion criteria, enabling us to best identify and study the utility of thiazide-like diuretics in our specific cohort of interest, notably patients with ADHF, renal insufficiency, and diuretic resistance. We opted for this study design instead of one of being all-inclusive and introducing post hoc statistical techniques such as propensity matching, a reasonable strategy, but one which has its own inherent limitations. Thus, caution should be used when extrapolating the results of this study to patients whose comorbid conditions excluded them from study entry (i.e., hypoalbuminemia). Also, a majority of patients in this study were African American. While this may reflect the demographic of patients at our medical center, an at-risk group for diuretic resistance, or both, this may limit the generalizability of our findings. Finally, because the vast majority of patients in this study had a reduced EF, these results may be less applicable to those with HF with a preserved EF.

Conclusions

In patients hospitalized with ADHF, renal insufficiency, and diuretic resistance receiving add-on thiazide-type diuretic treatment, there was no statistically significant difference in efficacy or safety between PO metolazone and IV chlorothiazide. While it is notable and perhaps even provocative that a numerically greater net increase in net and total UOP was observed in those receiving PO metolazone as compared to IV chlorothiazide, these results should be considered hypothesis-generating and not conclusive of equivalence. Thus, while our study suggests that either PO metolazone or IV chlorothiazide appears reasonable as add-on therapy in ADHF patients to combat diuretic resistance, we believe that our findings support the need for a large, randomized, multicenter head-to-head trial of add-on oral metolazone versus IV chlorothiazide whose major primary and secondary endpoints should include relevant clinical outcome measures such as death, hospital length of stay, recurrent ADHF hospital readmissions, and cost considerations.

Conflict of Interest

The authors declare no conflict of interest.

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None.

Author Contributions

Michael Moranville PharmD contributed to concept/design, data analysis/interpretation, data collection, drafting the article, critical revision of the article, and approval of article. Suji Choi PharmD contributed to concept/design, data analysis/interpretation, data collection, drafting the article, and approval of the article. Jennifer Hogg PharmD involved in data analysis/interpretation, drafting the article, and approval of the article. Allen Anderson MD participated in critical revision of the article and approval of the article. Jonathan Rich MD contributed to the concept/design, data analysis/interpretation, critical revision of the article, and approval of article.

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