Cardiology in the Young (2018), **28**, 27–31
doi:10.1017/S1047951117001330

Original Article

Enhancement of diuresis with metolazone in infant paediatric cardiac intensive care patients

Russell T. Wise,[1] Brady S. Moffett,[1,2] Ayse Akcan-Arikan,[2] Marianne Galati,[3] Natasha Afonso,[2] Paul A. Checchia[2]

[1]*Department of Pharmacy, Texas Children's Hospital;* [2]*Department of Pediatrics, Baylor College of Medicine, Houston, Texas, United States of America;* [3]*The Texas Medical Center Library, Houston, Texas, United States of America*

Abstract *Background:* Few data are available regarding the use of metolazone in infants in cardiac intensive care. Researchers need to carry out further evaluation to characterise the effects of this treatment in this population. *Methods:* This is a descriptive, retrospective study carried out in patients less than a year old. These infants had received metolazone over a 2-year period in the paediatric cardiac intensive care unit at our institution. The primary goal was to measure the change in urine output from 24 hours before the start of metolazone therapy to 24 hours after. Patient demographic variables, laboratory data, and fluid-balance data were analysed. *Results:* The study identified 97 infants with a mean age of 0.32 ± 0.25 years. Their mean weight was 4.9 ± 1.5 kg, and 58% of the participants were male. An overall 63% of them had undergone cardiovascular surgery. The baseline estimated creatinine clearance was 93 ± 37 ml/minute/1.73 m^2. Initially, the participants had received a metolazone dose of 0.27 ± 0.10 mg/kg/day, the maximum dose being 0.43 mg/kg/day. They had also received other diuretics during metolazone initiation, such as furosemide (87.6%), spironolactone (58.8%), acetazolamide (11.3%), bumetanide (7.2%), and ethacrynic acid (1%). The median change in urine output after metolazone was 0.9 ml/kg/hour (interquartile range 0.15–1.9). The study categorised a total of 66 patients (68.0%) as responders. Multivariable analysis identified acetazolamide use ($p = 0.002$) and increased fluid input in the 24 hours after metolazone initiation ($p < 0.001$) as being significant for increased urine output. Changes in urine output were not associated with the dose of metolazone ($p > 0.05$). *Conclusions:* Metolazone increased urine output in a select group of patients. Efficacy can be maximised by strategic selection of patients.

Keywords: Metolazone; loop diuretics; furosemide; paediatrics; intensive care

Received: 14 September 2016; Accepted: 28 May 2017; First published online: 11 September 2017

Background

Perioperative fluid overload reportedly increases patient morbidity and mortality.[1,2] Diuretics play an important role in maintaining fluid balance during both the preoperative and postoperative stages of management in children in the cardiovascular intensive care unit. Patients receiving long courses and high doses of single-diuretic therapy with loop diuretics such as furosemide may develop diuretic resistance, resulting in reduced urine output. The addition of diuretics that act on other sections of the nephron, such as thiazides, may increase urine output in this scenario.[3] It is common practice at the institution to add a thiazide diuretic to patients with low urine output who are concurrently receiving loop diuretic therapy to confer an additional mechanism on the renal tubules to increase urine output.

Metolazone, an oral thiazide diuretic, inhibits sodium reabsorption in the distal tubules, which causes increased excretion of sodium and water. Attending physicians in the paediatric cardiovascular

Correspondence to: B. S. Moffett, Pharm D, MPH, Department of Pharmacy, Texas Children's Hospital, 6621 Fannin Street, Suite WB1120, Houston, TX 77030, United States of America. Tel: 832 824 6087; Fax: 832 825 5261; E-mail: bsmoffet@texaschildrens.org

intensive care unit commonly use their discretion to administer metalazone, in addition to furosemide, to increase urine output. To date, no study conducted in paediatrics has evaluated the use of metolazone in paediatric cardiovascular intensive care patients.

This study seeks to evaluate the efficacy of adding metolazone to an established diuretic regimen in enhancing urine output and effecting electrolyte changes in critically ill infants admitted to a single-centre cardiovascular ICU. The hypothesis of this study is that the addition of metolazone to concurrent diuretic regimens increases urine output in paediatric cardiac intensive care patients.

Methods

The Institutional Review Board of the Baylor College of Medicine granted approval for conducting this retrospective cohort study. Data for analysis were extracted from the electronic medical records of the hospital and pertained to the period 30 June, 2013 to 29 June, 2015. The patients included in the cohort were less than a year old, had been admitted to the cardiac ICU at the institution, and had received metolazone. The study excluded patients whose fluid intake or output data were missing, or if they had been undergoing mechanical circulatory support or renal replacement therapy during the 24 hours before or after metolazone administration.

Data on the following patient demographic variables at the time of metolazone initiation were collected: serum sodium, serum creatinine, and other diuretic use. The Schwartz equation was used to calculate the estimated creatinine clearance.[4] Other data included loop diuretic doses both 24 hours before and 24 hours after metolazone initiation, along with fluid intake and output, and urine output.

We then calculated the overall change in urine output in millilitres per kilogramme per hour (ml/kg/hour) for the study population at 24 hours after the first dose of metolazone. An increase in urine output in the 24-hour after metolazone of $\geqslant 0.5$ ml/kg/hour was deemed clinically relevant. Patients who had this response – or "responders" – were compared with those who had a lower overall urine output – or "non-responders" – with regard to their demographic, laboratory, and medication variables.

Descriptive statistical methods – namely, mean, standard deviation, median, and interquartile range – were used to characterise the study population. Univariable methods such as the Student t-test, the Wilcoxon-Rank-Sum test, and the Fisher exact test were used to determine the differences between responders and non-responders. The study used multivariable linear regression analysis to determine the variables significant for change in urine output (ml/kg/hour) in the 24-hour period following metolazone administration, including the use of vasopressors, serum electrolytes, other diuretics, and serum creatinine. The analytical tool used was Stata IC v.12 (StataCorp, College Station, Texas, United States of America). An a priori p-value of <0.05 was considered significant.

Results

The cohort included 97 infants aged <1 year, of whom 58% were male. Their mean weight was 4.9 ± 1.5 kg. At the time of initiation of metolazone their mean age had been 0.32 ± 0.25 years. An overall 83% of the patients who had undergone cardiovascular surgery had received metolazone at median postoperative day 8 (range 2–126 days). Of the infants who had undergone cardiovascular surgery, 95% had been submitted to a cardiopulmonary bypass. Baseline sodium was 135 ± 5.3 mmol/L and baseline serum creatinine was 0.32 ± 0.16 mg/dl. Baseline estimated creatinine clearance at metolazone initiation was 93 ± 37 ml/minute/1.73 m^2.

The physicians initiated metolazone at a dose of 0.27 ± 0.10 mg/kg/day, with the maximum dose being 0.43 mg/kg/day. Patients received metolazone once a day, with the exception of five infants (5.2%), who received the drug every 12 hours. Other diuretics administered concomitantly with metolazone initiation included furosemide (87.6%), spironolactone (58.8%), acetazolamide (11.3%), bumetanide (7.2%), and ethacrynic acid (1%). No patient received hydrochlorothiazide or chlorothiazide. None received concomitant vasopressors either.

Overall, the median change in urine output in the 24-hour after metolazone administration was 0.9 ml/kg/hour (interquartile range 0.15–1.9). In all, 66 patients (68.0%) were categorised as responders (Table 1). The only variable significant on univariable analysis for a response to metolazone was urine output before the initiation of metolazone therapy (Table 1). A multivariable linear regression analysis for change in urine output (ml/kg/hour) over the 24-hour period after metolazone initiation identified acetazolamide use ($\beta = 1.1$, $p = 0.002$) and increased fluid input ($\beta = 0.013$, $p < 0.001$) during the same period as being significant for increasing urine output. Increased urine output in the 24-hour period before metolazone use correlated with decreased urine output after metolazone administration ($\beta = -0.02$, $p < 0.001$). No association existed between the dose of metolazone and changes in urine output ($p = 0.54$).

Graphically, no noticeable trend existed in the change in urine output on the basis of the dose of

https://doi.org/10.1017/S1047951117001330 Published online by Cambridge University Press

Table 1. Comparisons between metolazone responders and non-responders

Category (n = 97)	Non-Responder (<0.5 ml/kg/hour) (n = 31)	Responder (⩾0.5 ml/kg/hour) (n = 66)	p value
Age (years) (Mean, SD)	0.36 ± 0.27	0.36 ± 0.24	0.95
Cardiovascular surgery (%)	67.7	60.6	0.65
Baseline sodium (mmol/L)	135 ± 5.1	136 ± 5.4	0.53
Estimated creatinine clearance (ml/minute/1.73 m^2)	87 ± 31	97 ± 40	0.20
Input prior (ml/kg/day)	119 ± 29	99 ± 29	0.10
Input post (ml/kg/day)	111 ± 30	122 ± 33	0.14
Urine output before metolazone (ml/kg/hour)	4.2 ± 1.3	3.3 ± 1.1	<0.001
Metolazone dose (mg/kg/day)	0.27 ± 0.11	0.28 ± 0.10	0.56
Furosemide Prior (mg/kg/day)	3.7 ± 1.5	3.5 ± 1.6	0.61
Furosemide Post (mg/kg/day)	3.6 ± 1.7	3.4 ± 1.7	0.75
Bumetanide Prior (mg/kg/day)	0.02 ± 0.09	0.002 ± 0.04	0.21
Bumetanide Post (mg/kg/day)	0.009 ± 0.04	0.003 ± 0.02	0.40
Spironolactone (%)	64.5	56.1	0.51
Acetazolamide (%)	3.2	15.2	0.10

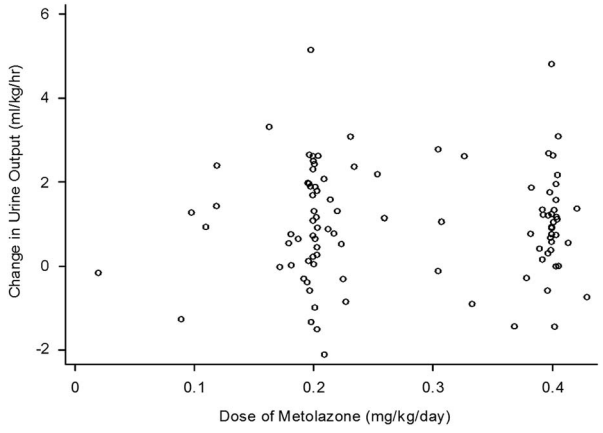

Figure 1.
Dose of metolazone and change in urine output.

metolazone (Fig 1). The median change in serum sodium from baseline to post-metolazone was 1.5 mEq/L (interquartile range 0–7.5 mEq/L). The difference in serum sodium change (4.1 ± 6.0 versus 4.5 ± 5.8 mEq/L, p = 0.76) and percentage serum sodium change (3.1 ± 4.5% versus 3.4 ± 4.3%, p = 0.67) in responders, compared with non-responders, was not significant. Similarly, there was no significant percentage change in serum creatinine (33 ± 80% versus 7 ± 30%, p = 0.10), potassium (0.1 ± 23.2% versus 3.9 ± 29.2%, p = 0.51), or bicarbonate (−4.8 ± 23.6% versus −8.7 ± 22.7%, p = 0.51) from the pre-metolazone period to the post-metolazone period when non-responders were compared with responders. Baseline bicarbonate values were not significantly different between non-responders and responders (29 ± 5 mEq/L versus 31 ± 5 mEq/L, p = 0.22). There was a statistically significant change in chloride (−9.3 ± 6.4% versus −5.6 ± 6.4%, p = 0.01), with non-responders demonstrating a greater change. There were no other adverse events.

Discussion

This is the first study to evaluate the effect of metolazone on urine output in infants in the paediatric cardiac ICU. A majority of the patients had clinically significant increases in urine output. This finding is relevant, as fluid overload in critically ill children is associated with increased morbidity and mortality, and effective methods of fluid mobilisation can improve patient outcomes.[1,2,5] Data from previous studies support this finding on the effects of metolazone in both adults and children.[6–13] Acetazolamide and metolazone have shown a benefit in adult patients in oedematous states who showed inadequate responses to loop diuretics. Metolazone noticeably improved urine output in infants who were receiving loop diuretics.[3,6,7,10] The use of metolazone in the infant population in the ICU appears to be warranted in select patients for increasing their urine output.

Interestingly, approximately one-third of the patients did not have a clinically relevant response. Other factors, such as kidney injury, concomitant use of vasopressors or inotropes, or alterations in serum electrolyte concentrations, are often present in critically ill infants, and can potentially alter metolazone efficacy. Despite an attempt by the study to account for these factors, other unknown factors may have limited the urine output response. One factor of significance was that patients who did not have a clinically relevant response had a higher baseline urine output. This suggests that the metolazone effect on urine output may have a ceiling, with further addition of metolazone no longer increasing

https://doi.org/10.1017/S1047951117001330 Published online by Cambridge University Press

the urine output. This is similar to the ceiling effect that loop diuretics demonstrate.[14] Similarly, on multivariable analysis, the use of metolazone resulted in increases in urine output when the fluid input was increased. This finding suggests that metolazone would be most beneficial in patients with increased total fluid intake and lowered urine output. Interestingly, the patients who responded had a greater fluid intake post metolazone administration. It is unclear whether this was due to the hypotension associated with diuresis or due to another factor that the study did not evaluate. Caution should be exercised to prevent intravascular depletion in patients on therapy with multiple diuretics.

The use of acetazolamide was also associated with an increase in urine output on multivariable analysis. As previously mentioned, acetazolamide demonstrably improves urine output in adult patients with inadequate responses to loop diuretics.[11] The effect of acetazolamide in this patient population is apparently additive to the effect of metolazone. This finding has implications for fluid removal in the infant cardiac population when selecting the best diuretic therapy. The researchers did not independently evaluate the use of acetazolamide; therefore, the conclusions that can be drawn from this finding are limited. On the basis of the data presented, the aetiology for the effect of acetazolamide in this patient population is unclear as bicarbonate values were not significantly different between non-responders and responders. The effect of acetazolamide on urine output in this population should be evaluated.

The limitations associated with this report are inherent to retrospective evaluations. The use of metolazone was attending-physician specific. The other diuretics, such as chlorothiazide and hydrochlorothiazide, had already been used at our institution. The assessment of kidney function included the estimation of creatinine clearance, but did not include an assessment of acute kidney injury. Urine output included measurements from both patients with and those without urinary catheters; thus, the measurement of urine could vary between that determined on the basis of catheter output volume and that determined on the basis of diaper weight. The study reviewed the use of only metolazone and hence it cannot comment on the efficacy of other diuretic regimens or practices that are commonly used in paediatric cardiac intensive care patients. Metolazone has been known to increase serum sodium, but we did not evaluate this aspect from a long-term perspective, as the data were collected only for a period of 24 hours after administration of a dose of metolazone. The absorption of metolazone may also be variable in the postoperative population, as they receive metolazone only through the enteral route. Patients who received continuous-infusion loop diuretic therapy with the addition of intermittent metolazone were not included in this study. Theoretically, the response rate to metolazone initiation may have been different had such patients been included. In addition, the use of loop diuretics with both metolazone and chlorothiazide may confer additional benefit in fluid mobilisation. Future directions in research should include prospective evaluations of diuretic therapy in the paediatric cardiac intensive care population.

Conclusion

Metolazone increased the urine output in a select group of infants in the paediatric cardiac intensive care unit. Patient selection should be based on stringent criteria and the goals of therapy should be well defined to maximise metolazone efficacy. Ideal patients for metolazone treatment should, perhaps, include those who do not achieve the desired urine output with loop diuretics and are able to tolerate oral administration of medications.

Acknowledgements

None.

Financial Support

This research received no specific grant from any funding agency, commercial enterprise, or not-for-profit sector.

Conflicts of Interest

None.

Ethical Standards

The authors assert that all the procedures that formed part of this study comply with the ethical standards of the relevant national guidelines on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The Baylor College of Medicine and Affiliated Institutions Institutional Review Board gave its approval for this study.

References

1. Selewski DT, Cornell TT, Blatt NB, et al. Fluid overload and fluid removal in pediatric patients on extracorporeal membrane oxygenation requiring continuous renal replacement therapy. Crit Care Med 2012; 40: 2694–2699.
2. Selewski DT, Cornell TT, Lombel RM, et al. Weight-based determination of fluid overload status and mortality in pediatric intensive care unit patients requiring continuous renal replacement therapy. Intensive Care Med 2011; 37: 1166–1173.

3. Sica DA, Gehr TW. Diuretic combinations in refractory oedema states: pharmacokinetic-pharmacodynamic relationships. Clin Pharmacokinet 1996; 30: 229–249.
4. Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. Pediatr Clin North Am 1987; 34: 571–590.
5. Arikan AA, Zappitelli M, Goldstein SL, Naipaul A, Jefferson LS, Loftis LL. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. Pediatr Crit Care Med 2012; 13: 253–258.
6. Arnold WC. Efficacy of metolazone and furosemide in children with furosemide-resistant edema. Pediatrics 1984; 74: 872–875.
7. Cachero SD, Lofland G, Springate JE, Feld LG. Combination of metolazone and furosemide in the treatment of edema in the first month of life. Child Nephrol Urol 1990; 10: 161–163.
8. Dargie HJ, Allison ME, Kennedy AC, Gray MJ. High dosage metolazone in chronic renal failure. BMJ 1972; 4: 196–198.
9. Dargie HJ, Allison ME, Kennedy AC, Gray MJ. Efficacy of metolazone in patients with renal edema. Clin Nephrol 1974; 2: 157–160.
10. Garin EH, Richard GA. Metolazone and furosemide therapy for edema. Pediatrics 1986; 77: 130–131.
11. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. J Am Coll Cardiol 2010; 56: 1527–1534.
12. Kshirsagar NA, Gupta KC, Paul T, et al. Effect of metolazone addition on furosemide resistant cases of edema. J Assoc Physicians India 1978; 26: 915–923.
13. Segar JL, Robillard JE, Johnson KJ, Bell EF, Chemtob S. Addition of metolazone to overcome tolerance to furosemide in infants with bronchopulmonary dysplasia. J Pediatrics 1992; 120: 966–973.
14. Oh SW, Han SY. Loop diuretics in clinical practice. E & BP 2015; 13: 17–21.