CLINICAL INVESTIGATION

Ethacrynic Acid Continuous Infusions in Critically Ill Pediatric Patients

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OBJECTIVES: The purpose of this study was to describe dosage regimens and treatment outcomes in critically ill children receiving ethacrynic acid continuous infusions (CI).

METHODS: This retrospective cross-sectional study evaluated patients less than 18 years of age who received ethacrynic acid CI with a duration exceeding 12 hours, from January 1, 2007, through January 31, 2012. The primary objective was to determine the mean/median doses of ethacrynic acid CI. Secondary objectives were to assess surrogate efficacy markers (e.g., urine output [UOP], fluid balance) and the number of patients with electrolyte abnormalities or metabolic alkalosis. Descriptive statistics were used. A series of repeated measures analyses of variance were conducted to assess differences in surrogate efficacy markers and in adverse events that occurred pre-, mid-, and posttherapy.

RESULTS: Nine patients were included. The mean $\pm$ SD initial and maximum doses (mg/kg/hr) were 0.13 ± 0.07 (median 0.1; range, 0.08-0.3) and 0.17 ± 0.08 (median, 0.16; range 0.09-0.3), respectively. The median UOP (mL/kg/hr) pre-, mid-, and postinfusions (interquartile range [IQR]) were 2.4 (1.8-3.2), 4.2 (3.5-6), and 4 (3.4-5.3), respectively. The median fluid balance (mL; IQR) was 189 (90-526), -258 (-411.7 to 249) and -113.5 (-212.5 to 80.2), respectively. There were statistically significant differences in UOP and fluid balance pre-versus mid-therapy (0.014) and pre- versus posttherapy ($p=0.010$). No significant differences were noted with magnesium and potassium. Five children (55.6%) developed metabolic alkalosis.

CONCLUSIONS: This study provides preliminary evidence for ethacrynic acid CI in children. The median initial dose and maximum dose in this cohort were 0.13 mg/kg/hr and 0.17 mg/kg/hr, respectively. Larger prospective studies are needed to confirm these findings.

INDEX TERMS: child, continuous infusion, ethacrynic acid, loop diuretics

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INTRODUCTION

Loop diuretic agents are often used in critically ill patients in the neonatal intensive care unit (NICU) and pediatric intensive care unit (PICU) for the management of volume overload and oliguria. These agents inhibit reabsorption of sodium and chloride in the ascending loop of Henle and distal renal tubule, resulting in diuresis that is more rapid and profound compared to other diuretic drug classes. Luciani et al¹ found that the administration of loop diuretics via continuous infusion (CI) produced a more controlled diuresis with less variation in hemodynamic parameters. Furosemide has been the most widely studied loop diuretic in regard to administration via CI in children.²⁻⁸ However, recent nationwide

shortages of injectable solutions of furosemide, bumetanide, and torsemide have occurred, thus forcing clinicians to explore other options for CI diuretic therapy.⁹ Guidance for dosing of other loop diuretics via CI is limited or non-existent. To date, only 1 study has provided preliminary data for bumetanide CI in children, and no studies have evaluated torsemide CI in this population.¹⁰

Ethacrynic acid is a loop diuretic agent that received US Food and Drug Administration (FDA) approval in 1967. It differs structurally from other loop diuretics because it does not contain a sulfonamide group within its structure.¹¹ Due to this structural difference, it is the loop diuretic of choice for children with life-threatening "sulfa" allergies. Ethacrynic acid has an FDA-labeled indication for treatment of edema in patients older

than 1 year of age.¹² Ethacrynic acid has been studied in pediatric patients in a single intravenous (IV) dose form and in multiple intermittent IV doses.^{13–16} These studies used a dose of 1 mg/kg/dose, consistent with that currently cited in available pediatric tertiary references.¹⁷ To date, no studies have evaluated the use of ethacrynic acid CI for ≥ 12 hours in pediatric patients, and no dosing recommendations exist. Because of the current shortages of other loop diuretic agents, there may be a need to use ethacrynic acid for CI. The purpose of this study was to describe dosage regimens and treatment outcomes in critically ill children receiving ethacrynic acid CI.

METHODS

Study Design

A descriptive, retrospective cross-sectional study was conducted to assess the use of CI ethacrynic acid in the PICU and NICU. This study was conducted at an academic pediatric hospital licensed for 230 inpatient beds; of which there are 88 NICU beds and 25 PICU beds. This study included patients younger than 18 years of age who received ethacrynic acid CI for more than 12 hours, from January 1, 2007, through January 31, 2012. After Institutional Review Board approval, patients were identified within the electronic database (Meditech; Medical Information Technology, Inc., Westwood, MA). Patients were excluded from the study if they received ethacrynic acid CI for less than 12 hours or they did not have complete medical records (e.g., if nursing flow sheets were unavailable).

Study Objectives and Data Collection

The primary objective of this study was to assess the mean and median doses of ethacrynic acid CI administered to children in the NICU and PICU. The secondary objective was to assess the effectiveness of the therapy using urine output (UOP) and fluid balance as surrogate markers. An additional secondary objective was to identify the number of children with electrolyte abnormalities or metabolic alkalosis, including those who required an intervention to treat the abnormality.

Baseline demographic data including sex, height, weight, admission diagnosis, ICU length of stay, and age at beginning of ethacrynic acid therapy were collected. For the ethacrynic acid regimens, data collection included duration

(hours), initial dose (mg/kg/hour), maximum dose (mg/kg/hour), cumulative dose (mg/kg), and number of dosing changes required. Additional data collected included the use of a diuretic therapy immediately prior to initiation of ethacrynic acid and adjunct diuretic therapy initiated while receiving ethacrynic acid CI. Laboratory parameters assessed pre-, mid-, and postethacrynic acid regimen included serum creatinine, blood urea nitrogen (BUN), serum electrolytes, UOP, and fluid balance. These values were obtained within 24 hours of initiation and discontinuation of ethacrynic acid therapy. If multiple laboratory values were collected within a 24-hour time frame, the values included for analysis were the closest to the 24-hour mark pre- and posttherapy. Glomerular filtration rate (GFR) was calculated during each time interval by using the Schwartz formula.¹⁸ Another proxy measure for ethacrynic acid therapy adverse events was the administration of an agent for the treatment of metabolic alkalosis (e.g., acetazolamide) or the replacement of magnesium or potassium.

Statistical Methods

Descriptive statistics were used to evaluate the results. All data management and statistics were performed using Stata version 10 software (Stata Corp., College Station, TX).¹⁹ To assess potential mean differences among the indicators of effectiveness (i.e., UOP, fluid balance, GFR) and adverse events at pre-, mid-, and postethacrynic acid CI, repeated measures analyses of variance (ANOVA) were conducted for each measure. The a priori level of significance was set at 0.05.

RESULTS

Patient Demographics

Eleven patients were identified for inclusion in the study. Two patients were excluded because the duration of their CI was less than 12 hours. Table 1 shows the baseline demographics for the 9 patients included in the study. The median age and weight of the patients were 1.3 years (range, 0.05–4.9 years) and 9.0 kg (2.1–17.0 kg). One patient was a full-term neonate who was started on ethacrynic acid on day-of-life 19. All 9 patients were initiated on ethacrynic acid therapy in the PICU. Six patients (66.7%) were diagnosed with a congenital heart defect and were admitted to the PICU status-post cardiothoracic surgery. The median (range) of ICU

Table 1. Baseline Demographics and Ethacrynic Acid Continuous Infusion Data

Pt	Age (yr) (weight)	Admission Diagnosis	Maximum Loop Diuretic CI Dose Prior to EA	Duration of Loop Diuretic CI Prior to EA (days)	Initial EA Dose (mg/kg/ hr)	Maximum EA Dose (mg/kg/hr)	Cumulative EA dose (mg/kg)	Duration of EA (hr)
1	4.9 (17 kg)	Toxic epidermal lytic necrosis	NA; pt with sulfa allergy	NA	0.09	0.09	8.5	98
2	1.74 (15.8 kg)	HLHS s/p Fontan completion; respiratory failure	0.25 /hr furosemide	6	0.13	0.13	18.6	184
3	0.41 (9 kg)	Respiratory failure; bilateral pneumothoraces, pneumomediastinum	0.22 mg/kg/hr furosemide	12	0.1	0.1	4.7	70
4	1.25 (12.9 kg)	Pulmonary atresia s/p repair; VSD s/p repair	0.28 mg/kg/hr furosemide	9	0.3	0.3	17.2	95
5	0.49 (7.41 kg)	Atrioventricular canal s/p repair	0.15 mg/kg/hr furosemide	15	0.1	0.22	41	382
6	1.58 (11.8 kg)	Influenza A infection; respiratory failure	NA; intermittent furosemide only	NA	0.1	0.1	1.7	51
7	0.052 (2.099 kg)	TOF s/p BT shunt and ECMO	0.15 mg/kg/hr bumetanide	10	0.08	0.16	6.5	42
8	0.2 (5.83 kg)	HLHS s/p Norwood- Sano procedure; respiratory failure	0.4 mg/kg/hr furosemide	9	0.089	0.27	10.3	74
9	4.32 (4.32 kg)	Truncus arteriosus s/p repair, VSD s/p repair	0.22 mg/kg/hr furosemide	11	0.19	0.19	8.38	61

BT, Blalock-Taussig shunt; CI, continuous infusion; EA, ethacrynic acid; ECMO, extracorporeal membrane oxygenation; HLHS, hypoplastic left heart syndrome; NA, not available; Pt, patient; s/p, status post; TOF, tetralogy of Fallot; VSD, ventriculoseptal defect

length of stay was 27 days (21-131 days).

All patients had previous exposure to loop diuretic therapy. Five patients (55.6%) received a loop diuretic CI, whereas 1 patient (11.1%) received intermittent IV loop diuretics. The remaining 3 patients (33.3%) received a combination of loop diuretics and thiazide diuretics (loop diuretic CI with intermittent IV chlorothiazide/ enteral metolazone [n=1] or loop diuretic CI with intermittent IV chlorothiazide [n=2]). The majority of patients (89%) were receiving diuretic therapy immediately prior to initiation of ethacrynic acid CI. For these patients, records indicated that ethacrynic acid was initiated secondary to poor clinical response to previous diuretic therapy. Only 1 patient had a documented sulfa allergy.

regimen of ethacrynic acid. The mean $\pm$ SD initial and maximum doses were 0.13 ± 0.07 mg/kg/hour (median 0.1 mg/kg/hour) and 0.17 ± 0.08 mg/kg/hour (median 0.16 mg/kg/hour), respectively. Three patients (33.3%) required 1 increase in dosage due to inadequate response. In addition, 2 patients (22.2%) required multiple increases of dosage (range, 2-4) in order to obtain an adequate response. Eight patients (88.9%) required at least 1 dosage decrease (range, 1-3). Most of those reductions in dose occurred when ethacrynic acid CI was being tapered toward the end of therapy. Only 2 patients (22.2%) required a decrease from the initial selected dose within the first 24 hours of use; both of these patients were initiated at a dosage of 0.1 mg/kg/hour.

Ethacrynic Acid Regimen

Table 1 also shows data regarding the dosing

Efficacy of Ethacrynic Acid Regimen

Table 2 describes surrogate markers of effec-

Table 2. Surrogate Markers of Efficacy and Adverse Events

Characteristic	Pre-Ethacrynic Acid CI*	Mid-Ethacrynic Acid CI*	Post-Ethacrynic Acid CI*	F	Post Hoc Analysis	p value†
<u>Markers of efficacy</u>						
UOP (mL/kg/hr)	2.4 ± 1.2‡	5.1 ± 3.1‡	4.5 ± 1.7§	5.72	Pre < Mid = Post	0.014
Fluid balance (mL)	403.5 ± 541.7‡	-161.0 ± 459.8‡	-77.0 ± 169.7§	6.38	Pre > Mid > Post	0.010
<u>Markers of adverse events</u>						
Glomerular filtration rate (mL/min/1.73 m ²)	129.6 ± 70.9‡	97.6 ± 55.5‡	89.6 ± 52.6‡	3.42	Pre = Mid = Post	0.058
BUN (mg/dL)	17.7 ± 13.1‡	23.0 ± 18.6‡	26.6 ± 24.8‡	0.75	Pre = Mid = Post	0.487
Potassium (mEq/L)	4.1 ± 0.77‡	3.4 ± 0.59‡	3.5 ± 0.79‡	2.20	Pre = Mid = Post	0.143
Sodium (mEq/L)	139.9 ± 2.1‡	141.7 ± 6.9‡	140.9 ± 8.1‡	0.43	Pre = Mid = Post	0.660
Chloride (mEq/L)	101.2 ± 7.0‡	99.3 ± 6.6‡	99.2 ± 9.8‡	0.32	Pre = Mid = Post	0.733
Magnesium (mEq/L)	2.1 ± 0.38‡	2.1 ± 0.51¶	2.2 ± 0.41‡	0.15	Pre = Mid = Post	0.864

CI, continuous infusion; UOP, urine output

* mean ± standard deviation

† Analysis was performed using repeated measures ANOVA

‡ n=9

§ n=8

¶ n=7

tiveness. UOP (mL/kg/hr) and fluid balance (mL) were collected pre-, mid-, and postinfusion. Patient number 7 expired, so UOP and fluid balance postethacrynic acid CI data were unavailable. The median UOP (mL/kg/hr) values at pre-, mid-, and postinfusion (interquartile ranges) were 2.4 (1.8-3.2), 4.2 (3.5-6), and 4 (3.4-5.3), respectively. The median fluid balance (mL) values (interquartile ranges) were 189 (90-526), -258 (-411.7 to 249), and -113.5 (-212.5 to 80.2), respectively. A repeated measures ANOVA revealed statistically significant differences in UOP and fluid balance pre- versus mid-therapy, as well as pre- versus post-therapy (Table 2).

Three patients (33.3%) required adjunct diuretic therapy while receiving ethacrynic acid CI. It was noted in the medical record that these patients had an inadequate response to ethacrynic acid CI alone. The adjunct diuretic agents included enteral metolazone (n=2), IV chlorothiazide (n=1), and IV furosemide (n=2).

Safety of Ethacrynic Acid Regimen

Table 2 also demonstrates various proxy indicators of adverse events. A number of different point-of-care measures were collected pre-, mid-, and postethacrynic acid CI to assess concerns for safety. Repeated measures ANOVAs were also used to assess differences across time periods. To

assess renal function, serum creatinine (mg/dL) and BUN (mg/dL) rates and estimated GFR (mL/min/1.73 m²) were evaluated. No significant differences were noted with BUN and GFR (Table 2).

To assess potential electrolyte abnormalities, serum sodium, potassium, magnesium, and chloride values were collected. Repeated measures ANOVAs revealed no statistically significant differences concerning all time points for all electrolytes assessed. Six patients (66.7%) required additional intravenous or enteral potassium supplementation. Patients who required potassium supplementation throughout their course of ethacrynic acid therapy received a mean ± SD dose of 5.7 ± 4.82 mEq/kg, with a median of 5.1 (1-13.5) mEq/kg. No patients required additional magnesium supplementation. Four patients (44.4%) received total parenteral nutrition during the ethacrynic acid therapy.

Five patients (55.6%) received a medication for treatment of metabolic alkalosis during therapy. Two patients (22.2%) received treatment with IV acetazolamide for 24 to 48 hours. Three patients (33.3%) received treatment with an IV arginine monohydrochloride infusion.

DISCUSSION

This retrospective, cross-sectional descriptive

study is the first to assess ethacrynic acid CI dosing in critically ill neonates and children. Ethacrynic acid is 30% less potent than furosemide and is associated with the greatest incidence of ototoxicity.¹¹ Much of the data for use of ethacrynic acid in children is from the late 1960s, using IV intermittent administration.^{13,15,16} Little has been published since that time, and no studies have evaluated CI.¹⁴ This is likely due to the introduction of other loop diuretic agents with greater potency and less ototoxic effects.

Ethacrynic acid is not commonly used as a CI in critically ill children; however, recent shortages of other loop diuretics have spawned the need to identify suitable alternatives for diuresis.⁹ Anecdotally, some clinicians may also consider using ethacrynic acid in patients with an inadequate response to another loop diuretic. In this study, 8 patients (88.9%) were initiated on ethacrynic acid due to an inadequate response to previous diuretic therapy. This is an interesting result, considering the reported differences in relative potency. Last, ethacrynic acid may be used in patients with a sulfa allergy because it does not contain a sulfonamide substituent. However, in this study, only 1 patient received ethacrynic acid for this indication.

Currently there are no pediatric studies which have evaluated ethacrynic acid CI dosing. We anecdotally noted that initial dosing for some patients was extrapolated by clinicians from the intermittent dose of 1 mg/kg/dose IV every 8 hours. This total daily dose (3 mg/kg/day) was divided by 24 hours to calculate a starting dose of 0.12 mg/kg/hour. This arbitrarily calculated dose was similar to that found for most patients with the initial mean $\pm$ SD of 0.13 ± 0.07 mg/kg/hr (median, 0.1; range, 0.08-0.3). There are a small number of studies which have evaluated the use of furosemide CI and bumetanide CI in children.^{2-8, 10} Doses of furosemide CI reportedly range from 0.05 to 0.4 mg/kg/hour and bumetanide CI doses from 0.001 to 0.2 mg/kg/hour. Given the relative potency reported in previous studies (i.e., furosemide is 30% more potent than bumetanide), the conversion of the reported furosemide CI doses to equipotent doses of ethacrynic acid CI would result in doses ranging from 0.035 to 0.28 mg/kg/hour. The mean and median maximum doses of 0.17 and 0.16 mg/kg/hour, respectively, reported in this study fall within this range of extrapolated doses. Only

1 patient received a dose outside of this range.

UOP and fluid balance were assessed pre-, mid-, and postethacrynic acid therapy to assess effectiveness of the CI. Based on the median UOP and fluid balance values during these time points, the ethacrynic acid CI was effective in increasing UOP and decreasing overall fluid balance. However, due to inadequate response to therapy, one-third of all patients received adjunct diuretic therapy while receiving ethacrynic acid CI. These patients received maximum doses of 0.13, 0.19, and 0.22 mg/kg/hour. Based on the previous calculation of doses equipotent to that of furosemide, none of these patients reached the extrapolated maximum dose of 0.28 mg/kg/hour. All 3 of these patients were receiving furosemide CI immediately prior to ethacrynic acid CI, and tolerance to diuretic effects has been reported for loop diuretics.²⁰ Therefore, it may be possible that higher doses might be needed in patients previously receiving another CI loop diuretic. Three other patients were receiving either furosemide or bumetanide CI immediately prior to initiation of ethacrynic acid; their maximum doses were 0.16, 0.27, and 0.3 mg/kg/hour. However, the sample size was too small to evaluate potential dose-response relationships.

Loop diuretics are commonly associated with adverse events including electrolyte abnormalities and development of metabolic alkalosis. Serum potassium, sodium, and chloride levels were collected pre-, mid-, and postethacrynic acid therapy to assess electrolyte effects. No significant changes during therapy were noted for any of the electrolyte measures (Table 2). Hypokalemia, hypochloremia, and hypomagnesemia can be expected with loop diuretics. It is possible that statistically significant changes were not observed in this study because 89.9% of the patients received diuretic therapy immediately prior to initiation of ethacrynic acid. Finally, it should be noted that two-thirds of patients did require IV potassium supplementation during the study period. Only 1 patient expired during ethacrynic therapy, but this death was attributed to the patient's underlying disease state and not related to ethacrynic acid or an electrolyte disturbance.

Hypochloremic metabolic alkalosis is a common complication of loop diuretic therapy because of loss of extracellular fluid and chloride. There was a numerical decrease in the chloride level noted before, during, and after ethacrynic

acid therapy. However, there were no statistically significant changes in chloride levels from beginning to end of therapy. It is possible that these results may be skewed because of low sample size and the fact that many patients had received diuretics prior to ethacrynic acid CI. Five of the patients received an agent for the treatment of metabolic alkalosis.

Due to the retrospective nature and small number of patients, there are inherent limitations with this study. By design, this was a descriptive study that focused on dosing of ethacrynic acid CI. We did not evaluate the rationale of why a specific dose was selected or the comparison of 1 dose versus another. Additionally, the retrospective collection of data for indicators of adverse effects and efficacy is limited in its focus. It is difficult to take into account the multiple factors that could affect these variables. For example, we evaluated only whether intermittent doses of potassium were administered but did not take into account the amount of potassium contained within the maintenance fluids or parenteral and enteral nutrition. In addition, ethacrynic acid has been reported to have an increased incidence of ototoxicity. We could not assess this adverse effect because this is not typically tested in the inpatient setting, other than in patients being discharged from the NICU. Additionally, this study included a small number of patients and did not allow for more robust statistical analyses to determine dose/effect relationships.

CONCLUSIONS

This descriptive, retrospective study provides preliminary evidence for selection of initial doses of ethacrynic acid CI in children. The median initial dose used in this cohort was 0.10 mg/kg/hour (range, 0.08-0.3 mg/kg/hour) with a median maximum dose of 0.16 mg/kg/hour (range, 0.09-0.3 mg/kg/hour). Further prospective studies are needed to better define appropriate ethacrynic acid CI initial and maximum doses in this population.

Disclosures The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

Abbreviations ANOVA, analysis of variance; BUN, blood urea nitrogen; CI, continuous infusion; FDA, Food and Drug Administration; GFR, glomerular filtration rate; IV, intravenous; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; UOP, urine output

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