Development of Tolerance to Chronic Intermittent Furosemide Therapy in Pediatric Patients

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OBJECTIVES The purpose of this study is to describe whether tolerance develops in pediatric patients receiving chronic intermittent furosemide therapy, to characterize when it occurs and whether age-related variations exist. The effects of increasing total daily dose of furosemide and concurrent diuretics and vasopressors were assessed as secondary aims.

METHODS Charts from patients receiving intravenous or oral furosemide for at least 3 consecutive days of therapy between June 1, 2013, and December 31, 2013, were reviewed retrospectively. Daily net fluid balance was used as the objective marker for development of tolerance. Net fluid balance (mL/kg/mg) was defined as the difference in a patient's daily intake and urine output (mL), normalized by weight (kg) and total daily dose of furosemide (mg).

RESULTS Sixty-one patients, aged 2 days to 20 years (median 3 years), were included in this study. Median daily dose of furosemide was 1.96 mg/kg/day (range, 0–13.7 mg/kg/day). Average net fluid balance for all patients on the first day and last day of therapy was 6.83 and 26.66 mL/kg/mg, respectively ($p = 0.011$). Linear regression and Spearman's correlation found no significant relationship between age and difference in net fluid balance between the first and last day. Linear mixed-effects model for net fluid balance with day as covariate found that net fluid balance increases over time ($p = 0.002$).

CONCLUSIONS Pediatric patients appear to develop tolerance to chronic intermittent furosemide therapy.

KEYWORDS diuretics; drug tolerance; furosemide; pediatrics; sodium potassium chloride symporter inhibitors

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Introduction

Furosemide is a loop diuretic frequently used in the pediatric population to manage fluid balance, both acutely and in chronic conditions such as heart failure. Despite its widespread use, pharmacokinetic and pharmacodynamic data to optimize use in the pediatric population are limited. In particular, the development of long-term tolerance to furosemide has been well described in adults, but data in pediatrics are limited.¹ Long-term tolerance is defined as the need to modify therapy to achieve the same diuretic response (i.e., increase dose and/or frequency, change or add diuretics). As patients develop tolerance and reach a therapeutic “ceiling,” providers are tasked with finding alternative methods to achieve fluid goals, while balancing adverse effects from medications. In current practice, the dose and/or frequency is typically increased as a first step towards overcoming tolerance. However, larger doses of furosemide may not result in significant diuresis, as suggested by its steep log dose-response curve.² Other methods to overcome tolerance include changing from intermittent dosing to a continuous infusion and/or

adding other agents.

The development of long-term tolerance to furosemide in adults is due to hypertrophy of distal nephron segments and increased sodium reabsorption.^{3,4} Although long-term tolerance has been well described in adults, data in pediatrics are limited and findings are mixed. For example, Eades and Christensen⁵ reported the development of tolerance to furosemide in 3 clinical trials involving pediatric patients on intermittent or continuous therapy.

Previous pediatric studies have focused on cardiac patients younger than 1 year. The first year of life is marked by significant developmental changes and cardiac patients often require fluid management post-operatively; thus, this patient population has been the focus of previous pediatric studies. For example, van der Vorst et al⁶ reported no development of tolerance or toxicity for post-cardiac surgery patients on continuous, large dose infusions of furosemide for 72 hours ($n = 15$).⁶ Although this may be a reasonable strategy in the acute postoperative period, patients requiring diuretic therapy for longer than 72 hours may need alternative strategies to manage fluid balance while

avoiding toxicity.

The purpose of this study is to describe whether long-term tolerance to chronic intermittent furosemide therapy develops in pediatric patients over a wide age cohort. Specifically, we set out to determine the onset and degree of tolerance and to identify whether age-related variations exist. Our secondary aims were to assess the effects of increasing the total daily dose of furosemide and concurrent diuretics and vasopressors on the development of tolerance.

Materials and Methods

This study is a retrospective, single center analysis of patients previously on intermittent intravenous or oral furosemide at Rady Children's Hospital, San Diego, California.

Patients. Patients receiving furosemide therapy between June 1, 2013, and December 31, 2013, at Rady Children's Hospital were identified via a clarity report generated through EPIC, the electronic medical record system. Patients ≤ 20 years of age were included if they had at least 3 consecutive days of intermittent intravenous or oral therapy. Patients without daily input and output data were excluded from the study. Patients were categorized on the basis of predetermined US Food and Drug Administration age groups; age groups were defined as follows: <1 month, 1 to 5 months, 6 to 11 months, 1 year, 2 to 4 years, 5 to 8 years, 9 to 12 years, 13 to 16 years, and 17 to 20 years of age. Initial patient selection was based on time of initiation of therapy to fulfill a minimum of 4 patients per age group. Thereafter, patients were preferentially selected on the basis of the longest duration of therapy. Data including demographic information, clinical variables, dosing history, concurrent medications, and net fluid balance were collected from electronic medical records.

Net Fluid Balance. Daily net fluid balance was used as the objective marker for the pharmacodynamic effect of furosemide. Net fluid balance (mL/kg/mg) was defined as the difference between a patient's daily intake and urine output (mL), normalized by weight (kg) and total daily dose of furosemide (mg).

Data Analysis. The change in net fluid balance between the first and last day of furosemide therapy was analyzed by using a paired *t* test. Spearman's correlation and a linear regression model were conducted to investigate the relationship between age and change in net fluid balance. Possible longitudinal effects were analyzed by using a linear mixed-effects model, with a random intercept and random slope over time included to account for intrasubject correlation, and with fixed covariates for day, age, and their interaction. Owing to the presence of wide interpatient variations in net fluid balance, the square root of net fluid balance was used as the dependent variable in the linear mixed-effects models to ensure that the distributional assumptions of the model were not violated. As a secondary aim, a

Table 1. Patient Demographic and Baseline Clinical Characteristics (n = 61)

Parameter	Value
Age*	3 yr (2 days–20 yr)
Weight, kg*	12.2 (0.8–111.3)
Serum creatinine, mg/dL*	0.3 (0.1–2.0)
Intravenous administration, %	76
Duration of therapy, days*	10 (3–60)
Clinical indications, n (%)	
Cardiovascular	29 (47)
Pulmonary	9 (15)
Neurological	8 (13)
Hematology/oncology	6 (10)
Musculoskeletal	4 (7)
Renal	2 (3)
Other	3 (5)

* Median (range).

binary effect was included for both concurrent diuretics and vasopressors in the mixed-effects model, as well as their interaction with day. Age was included as a fixed effect in each of these models as a controlling covariate. All analyses were done by using the R Statistical Programming Language (v. 3.2.2),⁷ and all linear mixed-effects models were fit with R package nlme.⁸

Results

Sixty-one patients, aged 2 days to 20 years (median 3 years), were included in this study. Patients varied in both clinical status (i.e., intensive care unit vs. medical/surgical unit) and indication for use of furosemide (Table 1). Twenty-nine of 61 patients (48%) were categorized with a cardiovascular indication for use. Other categories for indication included neurological, pulmonary, musculoskeletal, hematology/oncology, renal, and other. Median dose of furosemide was 1.96 mg/kg/day (range, 0–13.7 mg/kg/day). One patient had no change in total daily dose of furosemide for the duration of therapy. All other patients had at least 1 modification in total daily dose. Since patients had varying changes in furosemide therapy (i.e., increase, decrease, or no change), net fluid balance was normalized by total daily dose. Median duration of therapy was 10 days (range, 3–60 days). Table 1 summarizes the demographic and baseline characteristics of the study population, and Table 2 the age groups and distribution.

Average net fluid balance for all patients on the first day and last day of therapy were 6.83 and 26.66 mL/kg/mg, respectively ($p = 0.011$), suggesting that patients on chronic intermittent furosemide therapy become more fluid positive over time. A linear mixed-effects model was fit for net fluid balance with day as a covariate and

Table 2. Patient Age Groups and Distribution

Age Group	No. of Patients
<1 mo	14
1–5 mo	5
6–11 mo	6
1 yr	4
2–4 yr	10
5–8 yr	8
9–12 yr	5
13–16 yr	5
17–20 yr	4

resulted in a significant relationship where net fluid balance increases with increase in time as shown in Figure 1 ($p = 0.002$).

Linear regression and Spearman's correlation found no significant relationship between age and difference in net fluid balance between the first and last day of therapy ($p = 0.124$ and $p = 0.596$, respectively). However, a linear mixed-effects model for net fluid balance with day and age and their interaction as covariates found a significant relationship, where net fluid balance decreases with increasing age ($p = 0.002$).

Linear mixed-effects models for net fluid balance were fit with concurrent diuretics and vasopressors as covariates. In this study, 24 patients had at least 1 day of concurrent diuretic therapy, with an average duration of furosemide therapy of 12.74 days. Concurrent diuretics included acetazolamide, chlorothiazide, metolazone, and spironolactone. A significant relationship was found, with the presence of concurrent diuretics

decreasing net fluid balance ($p = 0.008$). A diuretic and day interaction was also estimated, and no interaction was found, indicating that the trend over time is not different between patients with and without concurrent diuretics ($p = 0.885$, Figure 2). Twelve patients had at least 1 day on vasopressors, with an average duration of furosemide therapy of 12.45 days. Vasopressors included dobutamine, dopamine, and norepinephrine. No significant relationship between day and vasopressors was found ($p = 0.703$). However, when fitting the model with a vasopressor and day interaction, we found a significant relationship where the trend over time is different between patients with and without vasopressors; patients on vasopressors have a decrease in net fluid balance over time ($p = 0.040$, Figure 3).

Discussion

Currently, there are insufficient data on the effects of chronic intermittent furosemide over time in pediatric patients. In adults, the development of tolerance is due to the hypertrophy of distal nephron segments with increased sodium reabsorption. The findings of this study support the development of tolerance in pediatric patients receiving chronic intermittent furosemide therapy, as reported by Eades and Christensen.⁵ Previous studies included only post-cardiac surgery patients in the first year of life, so patients with non-cardiac indications for furosemide therapy were included in this study to broaden the applicability of findings.

To identify age-related variations in tolerance, patients up to 20 years of age were included in this study. Linear regression and Spearman's correlation found no significant relationship between age and difference in net fluid balance between the first and last day of

Figure 1. Net fluid balance vs. time.

Figure 2. Net fluid balance vs. time with concurrent diuretics as a covariate.

therapy ($p = 0.124$ and $p = 0.596$, respectively). However, a linear mixed-effects model for net fluid balance with day and age as covariates found a significant relationship, where net fluid balance decreases with increasing age ($p = 0.002$). This suggests that the degree of tolerance is higher in younger patients than older patients.

The presence of concurrent diuretics such as hydrochlorothiazide or spironolactone resulted in a decrease in net fluid balance per day. This suggests that patients who are fluid overloaded despite optimal furosemide therapy may benefit from the addition of alternative diuretics in the short term. However, the results of the linear mixed-effects model suggest that patients who receive additional, concurrent diuretics when there is no longer a significant response to furosemide do not overcome the development of tolerance over time. Therefore, patients on chronic diuretic therapy may need alternative methods to maintain fluid balance.

In contrast, the presence of concurrent vasopressors did not have a significant effect on daily net fluid balance, but did have an effect on the degree of tolerance developed over time. Patients on concurrent vasopressor therapy had a decrease in net fluid balance over time as compared to patients without concurrent vasopressor therapy. Also, objective vital signs such as central venous pressure and mean arterial pressure were not collected as objective measures for fluid status.

As expected, we found that an increase in the total daily dose of furosemide resulted in a decrease in net fluid balance per day. However, an increase in total daily dose ultimately did not affect the trend over time, that is, the development of tolerance. This indicates that an increase in total daily dose is not enough to maintain neutral net fluid balance for a patient on chronic

therapy, as suggested by Prandota.² Thus, this study demonstrates the development of long-term tolerance in pediatric patients on chronic intermittent furosemide therapy. Future studies should focus on identifying strategies to best overcome tolerance.

There were several limitations to this study. It was retrospective in design and conducted at a single center. Owing to the retrospective design of the study, data such as urinary sodium or furosemide excretion were unavailable for analysis. Although each patient's overall net fluid balance was assessed to determine development of tolerance, provider-determined goals for fluid balance and/or urine output were not accounted for. Patients with varying clinical status and indication for use were included in the study to prevent limitation of results to a single patient population; however, in doing so, there is potential for significant interpatient variability. For example, a patient status post cardiac surgery will have a different fluid status and goal fluid balance than a patient who is edematous secondary to chronic kidney disease. Another limitation is that the age distribution of patients was not uniform. To address this limitation, we included age as a covariate throughout the models and found that there was no significant change in the results. Although the influences of concurrent diuretic and/or vasopressor therapies on the development of tolerance were analyzed, only a small number of patients were on concurrent therapies ($n = 24$ and $n = 12$, respectively). Therefore, doses of concurrent diuretics and/or vasopressors and vital signs associated with such therapies were not accounted for. Further studies including patients on concurrent diuretic and/or vasopressor therapy are needed to validate the effects these covariates were found to have in this study.

Figure 3. Net fluid balance vs. time with concurrent vasopressors as a covariate.

Conclusions

The development of tolerance is observed in pediatric patients receiving chronic intermittent furosemide therapy. The presence of concurrent diuretics decreases net fluid balance, but does not affect the trend over time. The presence of concurrent vasopressors dampens the effect of tolerance on net fluid balance over time, but does not have an immediate effect. An increase in dose causes a decrease in net fluid balance per day, but does not affect the trend over time.

ARTICLE INFORMATION

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