Increased Fracture Risk with Furosemide Use in Children with Congenital Heart Disease

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Objectives To determine the association of furosemide therapy with the incidence of bone fractures in children with congenital heart disease.

Study design We conducted a retrospective cohort study with data extracted from the 2008-2014 Texas Medicaid databases. Pediatric patients aged <12 years diagnosed with congenital heart disease, cardiomyopathy, or heart failure were included. Patients taking furosemide were categorized into a furosemide-adherent group (medication possession ratio of ≥70%), and a furosemide-nonadherent group (medication possession ratio of <70%). A third group of patients was matched to the furosemide user groups by using propensity score matching. A multivariate logistic regression and Cox proportional hazard model with a Kaplan–Meier plot (time-to-fracture) were used to compare the 3 groups, controlling for baseline demographics and clinical characteristics.

Results After matching, 3912 patients (furosemide adherent, n = 254; furosemide nonadherent, n = 724; no furosemide, n = 2934) were identified. The incidence of fractures was highest for the furosemide-adherent group (9.1%; 23 of 254), followed by the furosemide-nonadherent group (7.2%; 52 of 724), which were both higher than for patients who did not receive furosemide (5.0%; 148 of 2934) ($P < .001$). Using logistic regression, both furosemide groups were more likely to have fractures than the no furosemide group: furosemide-adherent OR of 1.9 (95% CI, 1.17-2.98; $P = .009$); furosemide nonadherent OR of 1.5 (95% CI, 1.10-2.14; $P = .01$). In the Cox proportional hazard model, the risk of fractures for the furosemide-adherent group was significantly higher compared with the no furosemide group (HR, 1.6; 95% CI, 1.00-2.42; $P = .04$).

Conclusions Furosemide therapy, even with nonconsistent dosing, was associated with an increased risk of bone fractures in children with congenital heart disease. *(J Pediatr 2018;■■:■■-■■).*

Furosemide, a potent diuretic, increases the urinary loss of potassium, calcium, and magnesium by inhibiting the passive reabsorption of these ions in the loop of Henle of the kidney.[1,2] Furosemide can thus cause hypercalciuria and nephrocalcinosis.[3] The excretion of calcium in the urine may cause a loss of bone mineral density, which can lead to osteoporosis.[4-6] An observational study indicated that for the adult population studied, any use of loop diuretics was associated with an increased risk of any fracture (crude 51% [odds ration (OR), 1.51; 95% CI, 1.48-1.55]; adjusted 4% [OR, 1.04; CI, 1.01-1.07]).[7] In a meta-analysis that studied the association between loop diuretic uses and the risk of fractures for adult patients, compared with nonloop diuretic users, loop diuretics users had an approximately 15% higher risk of total fractures.[8]

Furosemide is less commonly prescribed in children than adults. Specific children, including those with congenital heart defects (CHD), have a higher use of this medication.[1] More specifically, in children who have CHD and cardiomyopathies, diuretics often are given to treat symptoms of heart failure.[9] However, given studies conducted in adults with furosemide use, concerns remain about loop diuretics, particularly with chronic use, for children. Furosemide is specifically related to higher rates of hypercalciuria.[10] Atkinson et al reported that treatment with any type of diuretic in infants was associated with an abnormal renal loss of calcium, sodium, chloride, and potassium and others have cautioned that children with CHD or who have cardiomyopathy and who are prescribed loop diuretics may be at particular risk for developing metabolic bone disease.[11]

The purpose of this study was to determine the association of furosemide therapy with fractures in children with CHD.

Methods

Data were extracted from the Texas Medicaid Database, which consists of insurance claims that include demographic, medical, and prescription claims between January 1, 2008 and December 31, 2014. The Texas Medicaid program provides

CHD	Congenital heart defect
HR	Hazard ratio
ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
MPR	Medication possession ratio
PPIs	Proton pump inhibitors

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health insurance coverage for low-income families, individuals with chronic disabilities, blind persons, low-income pregnant women, elderly people or seniors, nondisabled children, and caretakers of dependent children. Medicaid enrollment in the state of Texas for clients <21 years of age is approximately 3 million for 2016.[12]

The study was approved by the University of Texas at Austin Institutional Review Board and by the Texas Health and Human Services Commission. The following information was extracted from the Texas Medicaid database: date of birth, sex, race/ethnicity, start and end dates of health plan enrollment, *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic codes, Healthcare Common Procedure Coding System codes, service dates, quantity of the medication dispensed, the number of days of supply, National Drug Code, Generic Sequencing Number, and American Hospital Formulary Service number.

Study Design

A retrospective cohort study design was used to assess the association of furosemide use and fractures. Both inpatients and outpatients were included in the study if they were <12 years of age and had ≥1 claim with a diagnosis of CHD, cardiomyopathy, or heart failure. Many patients were diagnosed as infants; therefore, 1 year of previous use before the index date was not required, but all were required to have ≥1-year of follow-up data (ie, be enrolled and using services) past their medication index date. Patients were excluded if the first date for a diagnosis claim for CHD, cardiomyopathy, or heart failure occurred after the medication index date. In addition, if patients had any claims for diuretic prescriptions or ICD-9-cardiomyopathy codes for fractures on or before their medication index date they were also excluded from analysis. The study timeframe was described in **Appendix 1** (available at www.jpeds.com).

Under the assumption that a patient used furosemide chronically, those who met study criteria were divided into 3 groups.

Furosemide-Adherent Group. The date of the first prescription for furosemide was considered the patient's medication index date. If the patient had at least 256 days of furosemide prescriptions during the first year post-index (ie, medication possession ratio [MPR] of ≥ 70%), they were categorized into the furosemide-adherent group. A wide range of cutoff adherence values for the MPR (63%-89%) have been used in previous adherence studies.[13] However, the MPR cutoff of 70% was used for this study based on the distribution of adherence in this sample (ie, natural break). A sensitivity analysis was conducted to validate the base model using the more commonly used 80% cutoff MPR.

Furosemide-Nonadherent Group. Again, the date of the first prescription for furosemide was considered the patient's medication index date. If the patient had <256 days of furosemide prescriptions during the first year postindex (ie, a MPR of <70%), they were categorized into the furosemide-nonadherent group.

No Furosemide Group. If patients did not have a furosemide prescription at any time, but had another diuretic prescription, their index date was defined as the first date of this diuretic prescription fill. The other type of diuretics included potassium-sparing diuretics and thiazide diuretics. If patients did not have any prescriptions for diuretics, a random index date was generated from the list of medication fill dates for that patient within one year from the first prescription claim date. Patients with nonfurosemide diuretics or no diuretics were combined to form the no furosemide group.

Study Outcomes and Covariates

The primary outcome was the new occurrence of a bone fracture within the postindex period. To control for other factors that might be associated with the incidence of fractures, additional variables were included as covariates in the multivariate analyses. First, patients were divided into those who only had a CHD diagnosis and those that had either a cardiomyopathy and/or heart failure diagnosis in addition to a CHD diagnosis. Second, 2 diseases indicators were selected as covariates to assess comorbidity: a diagnosis of bronchopulmonary dysplasia (ICD-9-CM 770.7) and a diagnosis of low birth weight or prematurity (ICD-9-CM 764.x, 765.x). Next, clinical factors were included to adjust severity of disease: heart-related surgery (eg, heart surgery, aortic valve repair) and use of proton pump inhibitors (PPIs; ie, omeprazole, esomeprazole, lansoprazole, rabeprazole, pantoprazole, and dexlansoprazole), which have also been shown to increase fracture risk.[14-16] In addition, the use of less commonly used medications—H2-antagonist, beta-blockers, and calcium or vitamin D supplementation—were added in a sensitivity analysis. These agents were identified only when their claims were found between the first date of diagnosis of CHD, cardiomyopathy, or heart failure and the first date of the occurrence of a fracture. For those who did not have any fractures in the study period, a random date within 1 year from the index date was used instead of first fracture date. In addition, other demographic factors included in the model were age at index date; sex; and race/ethnicity (white, black, Hispanic, and others [Asian, Native Hawaiian, or uncategorized race]). The detailed ICD-9-CM codes for CHD, cardiomyopathy, heart failure, and fractures used in this study are described in **Appendix 2** and **Appendix 3** (available at www.jpeds.com).

Statistical Analyses

Baseline characteristics and treatment variables were compared using χ^2 tests for all categorical variables and ANOVA tests for all continuous variables. Matching was performed using the propensity score matching method to reduce the bias in covariates among 3 groups. Propensity scores were generated using logistic regression and the matching used a greedy algorithm, which uses the nearest available pair matching methods.[17] Covariates used for logistic regression included all covariates as described, including both demographic and clinical factors. The incidence of fracture occurrence was compared among groups using χ^2 tests. To estimate the odds of a fracture in the study population, a logistic regression of the

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