Seguridad de Enalapril en lactantes admitidos en la Unidad de Cuidados Intensivos Neonatales.

Lawrence C. Ku y colas- Pediatr Cardiol (2017) 38:155–161

Cardiología Pediátrica 2017; Vol. 38 (1): 155 161

Enalapril se utiliza para tratar la hipertensión y la insuficiencia cardíaca congestiva en los lactantes. Sin embargo, el enalapril no está etiquetado para neonatos, y los datos de seguridad en los niños son escasos.

Para evaluar la seguridad del enalapril en lactantes, se realizó un estudio retrospectivo de cohorte de lactantes que fueron expuestos a enalapril en los primeros 120 días de vida y se atendieron en 348 unidades de cuidados intensivos neonatales de 1997 a 2012. Determinamos la proporción de Los niños expuestos que desarrollaron eventos adversos, incluyendo muerte, hipotensión que requieren presores, hipercaliemia y creatinina sérica elevada. Utilizando la regresión logística multivariable, se examinaron los factores de riesgo de eventos adversos, incluyendo la edad postnatal a la primera exposición, la duración de la exposición, el grupo de edad gestacional,

De una cohorte de 887.910 lactantes, 662 lactantes (0,07%) fueron expuestos a enalapril. Entre los lactantes expuestos, 142 infantes (21%) sufrieron un evento adverso. El evento adverso más frecuente fue hiperkalemia (13%), seguido por creatinina sérica elevada (5%), hipotensión (4%) y muerte (0,5%). Los factores de riesgo significativos para los eventos adversos incluyeron la edad postnatal <30 días a la primera exposición y la duración más larga de la exposición. Este estudio es el más grande hasta la fecha examinando la seguridad de enalapril en recién nacidos a término y prematuros sin enfermedad cardiaca estructural significativa.

Pediatr Cardiol (2017) 38:155–161
DOI 10.1007/s00246-016-1496-2

ORIGINAL ARTICLE

Safety of Enalapril in Infants Admitted to the Neonatal Intensive Care Unit

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Received: 10 June 2016 / Accepted: 25 October 2016 / Published online: 8 November 2016

Abstract Enalapril is used to treat hypertension and congestive heart failure in infants. However, enalapril is not labeled for neonates, and safety data in infants are sparse. To evaluate the safety of enalapril in young infants, we conducted a retrospective cohort study of infants who were exposed to enalapril in the first 120 days of life and were cared for in 348 neonatal intensive care units from 1997 to 2012. We determined the proportion of exposed infants who developed adverse events, including death, hypotension requiring pressors, hyperkalemia, and elevated serum creatinine. Using multivariable logistic regression, we examined risk factors for adverse events, including postnatal age at first exposure, exposure duration, gestational age group, small for gestational age status, race, sex, 5-min Apgar score, and inborn status. Of a cohort of 887,910 infants, 662 infants (0.07%) were exposed to enalapril. Among exposed infants, 142 infants (21%) suffered an adverse event. The most common adverse event was hyperkalemia (13%), followed by elevated serum creatinine (5%), hypotension (4%), and death (0.5%). Significant risk factors for adverse events included postnatal age <30 days at first exposure and longer exposure duration. This study is the largest to date examining the safety of enalapril in young term and preterm infants without significant structural cardiac disease.

Keywords Enalapril · Drug safety · Infant pharmacology · Pharmacoepidemiology

Introduction

Enalapril is an angiotensin-converting enzyme (ACE) inhibitor used to treat hypertension and congestive heart failure in infants [1–4]. The drug is approved by the Food and Drug Administration for treatment of hypertension in infants and children age 1 month to 16 years [5]. Among infants hospitalized in a neonatal intensive care unit (NICU), the overall incidence of hypertension is estimated to be 0.8–1.3% [6]. When risk factors such as bronchopulmonary dysplasia, patent ductus arteriosus, intraventricular hemorrhage, or umbilical arterial catheterization are present, the incidence of hypertension can be as high as 9% [7, 8]. In the NICU, enalapril is used to treat hypertension in up to 20% of cases [6].

Safety data in term and preterm infants are lacking, however. Studies evaluating the safety of enalapril in infants are limited to subjects with known single-ventricle physiology and other congenital cardiac defects [9, 10]. Among adults and children treated with enalapril, adverse events (AEs) include acute renal failure, hypotension, azotemia, hyperkalemia, cough, and angioedema, with the incidence of overall AEs ranging from 11 to 58% [5, 11–17]. The incidence of these AEs in young infants is poorly described.

The objectives of this study were to use electronic health record data to characterize the safety profile of enalapril in young term and premature infants without significant congenital heart disease, and to examine the risk factors for AEs occurring during enalapril exposure.

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Methods

Subjects

We identified all infants exposed to enalapril in the first 120 days of life and discharged from 348 NICUs managed by the Pediatrix Medical Group from 1997 to 2012. Data were obtained from an electronic medical record that contains information used to produce admission, daily progress, and discharge notes for all infants during their hospitalization. Infants who died on or before 7 days of life or had significant congenital anomalies were excluded. Congenital anomalies were considered significant if they were lethal, life-shortening, or life-threatening, required major surgery, or significantly reduced quality of life [18]. This definition also resulted in the exclusion of infants with significant congenital heart disease. Because congenital anomalies are strongly associated with infant mortality and morbidity, we excluded these infants to reduce potential confounding [19].

Definitions

We defined exposure as receiving 1 or more days of enalapril in the first 120 days of life. The duration of a single course of exposure was defined as the number of continuous days an infant received enalapril. Infants with known start day for exposure to enalapril but unknown end day were assumed to have started and stopped the medication on the same day. AEs of interest included death; hypotension requiring vasopressor therapy with dopamine, dobutamine, epinephrine, or norepinephrine; hyperkalemia (serum potassium $>$ 6 mmol/L); and elevated serum creatinine ($\geq$1.3 mg/dL). These AEs were selected based on AEs previously reported in older populations [5, 11–17]. We considered an AE to be associated with exposure to enalapril if an infant died, had a new diagnosis of hypotension requiring vasopressor therapy, or developed hyperkalemia or elevated serum creatinine on any day that enalapril was received. Preexisting hypotension was not counted as an enalapril-associated AE and was defined as having hypotension on the day before and the first day of enalapril exposure. The composite outcome was defined as having one or more AEs of interest occur during exposure to enalapril.

Statistical Analysis

For the composite and individual outcomes of death, hypotension requiring pressors, hyperkalemia, and elevated serum creatinine, we determined the proportion of infants who were affected during treatment with enalapril at the course level. We used the Kruskal–Wallis one-way analysis of variance test with Dunn's test of multiple comparisons to compare postnatal ages on first exposure across gestational age groups. We used multivariable logistic regression to examine risk factors for adverse events at the course level in only infants on enalapril, including for postnatal age on first exposure, exposure duration, gestational age group, small for gestational age status, race, sex, 5-min Apgar score, and inborn status.

We controlled for baseline potassium levels while evaluating hyperkalemia, baseline creatinine levels while evaluating elevated serum creatinine, and baseline potassium and creatinine levels while evaluating the composite outcome. Baseline levels were defined as the most recently observed value prior to first exposure to enalapril and were included in the regression models as continuous variables.

Statistical analyses were performed using Stata 13.1 (College Station, TX). All tests were 2-sided comparisons with $p < 0.05$ considered to be significant. Approval for this study was obtained from the Duke University Institutional Review Board.

Results

From a cohort of 887,910 infants, we identified 662 (0.07%) infants who were exposed to enalapril during their initial hospitalization. Enalapril was prescribed at only 106 (30%) sites (Fig. 1). Its use remained relatively constant during the study period, with enalapril used in 0.03–0.09% infants from 1997 to 2002 and in 0.07–0.10% infants from 2003 to 2012. The median gestational age of the exposed infants was 30 weeks (25th, 75th percentiles: 27, 36) (Table 1). The median birth weight was 1345 g (910, 2700), and 56% of infants were very low birth weight (<1500 g). Of the infants exposed to enalapril, 94% received only one course of enalapril. The median length of hospital stay for all exposed infants was 64 days (27, 103).

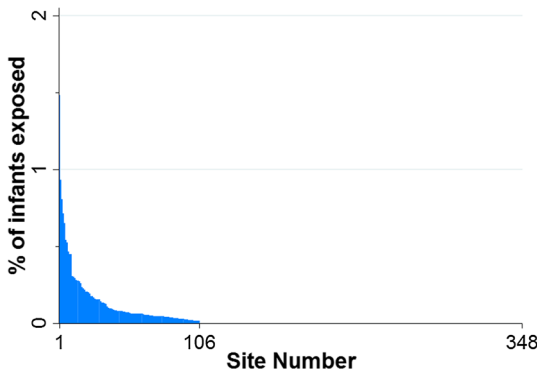

Fig. 1 Enalapril use by site during 1997–2012

Table 1 Demographics and baseline characteristics

	Number of exposed infants (%) ($N = 662$)
Gestational age,[a] weeks	
<28	204 (31)
28–33	219 (33)
>33	238 (36)
Birth weight,[b] g	1345 (910, 2700)
Male	377 (57)
Race/ethnicity	
White	308 (47)
Black	109 (16)
Hispanic	187 (28)
Other	28 (4)
Unknown	30 (5)
Inborn[c]	417 (63)
Small for gestational age[d]	98 (15)
5-min Apgar score[e]	
0–3	48 (7)
4–6	106 (16)
7–10	477 (72)
Postnatal age at first exposure,[b] days	25 (10, 78)
<28 weeks' gestational age	88 (58, 101)
28–33 weeks' gestational age	37 (11, 68)
>33 weeks' gestational age	11 (7, 19)
Postmenstrual age at first exposure,[b] weeks	38 (35, 40)
<28 weeks' gestational age	38 (34, 40)
28–33 weeks' gestational age	35 (32, 39)
>33 weeks' gestational age	39 (38, 42)
Exposure duration,[b] days	3 (1, 8)

[a] Missing data for 1 infant

[b] Data presented as median (25th, 75th percentiles)

[c] Missing data for 4 infants

[d] Missing data for 2 infants

[e] Missing data for 31 infants

The median postnatal age at which infants were first exposed to enalapril was 25 days (10, 78), with a median duration of exposure of 3 days (1, 8). First exposure occurred at significantly older median postnatal ages in infants born at <28 weeks' gestational age, 88 days (58, 101), compared to infants born at 28–33 weeks' gestational age, 37 days (11, 68), $p < 0.001$, and >33 weeks' gestational age, 11 days (7, 19), $p < 0.001$. The most common concomitant medications included vancomycin (81/662 [12%]), furosemide (71/662 [11%]), gentamicin (49/662 [7%]), hydralazine (47/662 [7%]), and captopril (38/662 [6%]) (Table 2).

A total of 142 infants (21%) experienced the composite outcome of death, hypotension requiring pressors, hyperkalemia, or elevated serum creatinine during exposure to enalapril (Table 3). The most common adverse event was hyperkalemia (13%), followed by elevated serum creatinine (5%), hypotension (4%), and death (0.5%). Significant risk factors for the composite outcome included postnatal age <30 days during first exposure to enalapril, and longer exposure duration (Table 4). Infants <30 days' postnatal age at first exposure were more likely to experience hyperkalemia, elevated serum creatinine, and hypotension. Longer durations of exposure to enalapril were associated with increased odds of hyperkalemia and death, but not elevated creatinine or hypotension. Other significant risk factors identified for individual AEs include black and other (non-white, non-Hispanic) races for hyperkalemia. In a sensitivity analysis, we controlled for concomitant hydralazine therapy during enalapril therapy and observed similar results (data not shown). The paucity of death outcomes ($n = 3$) resulted in model overfitting

Table 2 Top 10 concomitant medications

	Number of exposed infants (%) ($N = 662$)
Vancomycin	81 (12)
Furosemide	71 (11)
Gentamicin	49 (7)
Hydralazine	47 (7)
Captopril	38 (6)
Ranitidine	36 (5)
Cefotaxime	32 (5)
Ampicillin	31 (5)
Morphine	31 (5)
Phenobarbital	28 (4)

Table 3 Adverse events during enalapril exposure

	Number of exposed infants (%) ($N = 662$)
Hyperkalemia	83 (13)
Elevated creatinine	34 (5)
Hypotension	25 (4)
Death	3 (0.5)
Composite outcome	142 (21)

and precluded the analysis of risk factors for death during enalapril exposure.

Discussion

This study is the largest to date examining the safety of enalapril in young term and preterm infants without significant structural cardiac disease. Approximately one in five infants exposed to enalapril experienced at least one AE during treatment, with hyperkalemia being the most common AE. Among infants without congenital anomalies such as congenital heart disease, death during enalapril therapy was extremely rare. Exposure during the first 30 days' postnatal age and treatment duration were significant predictors for development of at least one AE.

Compared to infants first exposed beyond 30 days' postnatal age, infants with exposure to enalapril during the neonatal period were more likely to develop hyperkalemia and elevated serum creatinine, which are commonly observed side effects in adults with ACE inhibitor-induced acute renal failure [20]. Mechanisms observed in ACE inhibitor-induced acute renal failure and related AEs such as hyperkalemia and elevated creatinine in adults include volume depletion from concomitant diuretic therapy and chronic renal insufficiency [20]. In many cases, hyperkalemia in adults will resolve despite continued therapy at the same or lowered doses [5, 21]. Similar mechanisms might explain the increased risk for renal AEs such as elevated creatinine and hyperkalemia seen in enalapril exposure during the neonatal period. At birth, reduced renal blood flow and increased renal vascular resistance result in a decreased glomerular filtration rate compared to older infants [22]. In term and preterm infants, glomerular filtration rate rapidly increases over a 2-week period after birth, coinciding with a robust diuresis and natriuresis that occurs regardless of fluid intake amount [23]. Decreased initial renal function coupled with an increased risk for hypovolemia could lead to the increased risk for renal AEs seen in neonates exposed to enalapril.

Because elimination of enalapril and its active metabolite enalaprilat is primarily renal, reduced kidney function leading to increased exposures could potentially explain why infants age <30 days are at increased risk for other AEs such as hypotension [5]. In a study of enalapril and enalaprilat pharmacokinetics in 12 subjects age 10 days to 6.5 years with congestive heart failure, mean-area-under-the-curve values of active metabolite per enalapril dose normalized for body weight and body surface area were fivefold greater in the three subjects age <20 days compared to subjects >20 days old [24]. This suggests that infants <20 days old would require a significantly lower dose than their older counterparts, though larger studies are necessary before definitive conclusions can be made.

The renin–angiotensin system plays a crucial role during nephrogenesis, which does not complete until 34 weeks' gestational age [25, 26]. Consequently, antagonism of this system prior to completion of nephrogenesis by ACE inhibitors such as enalapril can lead to acute fetal and neonatal renal dysfunction, which can result in hypotension, renal failure, anuria, and death [3, 5, 27–31]. Interruption of the renin–angiotensin system during nephrogenesis may even result in renal dysmorphisms and dysfunction that persist into adolescence [32]. Though evidence is scant, current recommendations are to avoid ACE inhibitors in infants before 44 weeks' postmenstrual age [7]. This explains the observation in this study that infants born at younger gestational ages were more likely to be exposed to enalapril at older postnatal ages. The majority of infants born at <28 weeks' gestational age were first exposed to enalapril after 60 days' postnatal age. In our study, when analysis was restricted to only infants exposed to enalapril before 44 weeks' postmenstrual age, the regression results were similar for all AEs except for hypotension, in which postnatal age <30 days was no longer a significant risk factor.

Hypotension, acute renal failure, decreased urine output, and azotemia associated with use of enalapril have been reported in preterm and term infants [33–36]. Larger studies have focused predominantly on infants with

Table 4 Predictors for adverse events during enalapril exposure

	Hyperkalemia[a]	Elevated creatinine[b]	Hypotension	Composite outcome[c]
Postnatal age, days				
<30	**2.47 (1.19–5.12)**	**11.1 (2.72–45.3)**	**15.6 (1.30–189)**	**4.85 (2.51–9.38)**
30–60	1.77 (0.61–5.17)	4.05 (0.61–27.1)	3.08 (0.16–60.0)	2.21 (0.91–5.41)
61–120	Ref	Ref	Ref	Ref
Duration of exposure, days	**1.08 (1.05–1.10)**	1.00 (0.95–1.04)	0.97 (0.92–1.03)	**1.06 (1.03–1.08)**
Gestational age, weeks				
<28	0.61 (0.26–1.41)	2.44 (0.81–7.37)	1.31 (0.29–5.88)	0.98 (0.48–1.97)
28–33	0.88 (0.43–1.78)	1.67 (0.66–4.26)	1.03 (0.37–2.86)	0.87 (0.48–1.60)
>33	Ref	Ref	Ref	Ref
Small for gestational age				
Yes	0.98 (0.49–1.98)	1.51 (0.52–4.41)	1.01 (0.30–3.43)	1.33 (0.71–2.50)
Race/ethnicity				
White	Ref	Ref	Ref	Ref
Black	**3.12 (1.51–6.46)**	1.67 (0.53–5.23)	0.24 (0.03–2.04)	1.60 (0.84–3.05)
Hispanic	1.02 (0.49–2.13)	1.89 (0.78–4.58)	0.98 (0.38–2.52)	1.33 (0.76–2.34)
Other	**3.98 (1.34–11.8)**	1.99 (0.36–11.0)	1.15 (0.26–5.14)	1.59 (0.56–4.55)
Sex				
Male	1.37 (0.75–2.50)	0.76 (0.34–1.68)	1.22 (0.51–2.92)	1.16 (0.72–1.89)
5-min Apgar score				
0–3	1.59 (0.72–3.52)	1.10 (0.27–4.41)	0.99 (0.18–5.37)	1.74 (0.83–3.68)
4–6	0.86 (0.35–2.10)	0.59 (0.17–2.11)	1.63 (0.55–4.87)	0.94 (0.46–1.90)
7–10	Ref	Ref	Ref	Ref
Inborn				
Yes	0.84 (0.46–1.55)	1.03 (0.43–2.47)	0.53 (0.23–1.21)	0.76 (0.45–1.26)

Bold values indicate statistically significant at $p < 0.05$

Data presented as odds ratio (95% confidence interval). Death during enalapril exposure was a rare outcome, and regression could not be performed due to model overfitting

[a] Regression controlled for baseline potassium level prior to exposure

[b] Regression controlled for baseline creatinine level prior to exposure

[c] Regression controlled for baseline potassium and creatinine levels prior to exposure

significant congenital heart disease, a population already at increased risk for acute renal injury and other morbidities secondary to cardiac insufficiency and specialized cardiac procedures [9, 10]. A multicenter, randomized trial on enalapril use in young infants with single-ventricle physiology involving 230 term infants found no significant difference in the number of adverse events between treatment and placebo groups [9]. In a retrospective study of 206 preterm and term neonates with various cardiovascular diseases, including structural heart defects, infants had significant dose-independent decreases in creatinine clearance and elevations in serum potassium during exposure to an ACE inhibitor (enalapril or captopril) [10].

An interesting observation in our study was the apparent concomitant administration of captopril with enalapril in 38 infants. In almost all cases, concomitant administration occurred for only 1 day at the end of the course for one drug and at the beginning of the course for the other drug. This suggested that the infant was being switched from one ACE inhibitor to another ACE inhibitor, but the reason for this change in therapy is unknown.

Our study demonstrated substantial variability in enalapril use by NICU hospitalized infants among sites. Significant variation in use across sites is not unique to enalapril and has been described for many other drugs used in the NICU [37–40]. Many drugs used in infants are used off-label, with inadequate safety, efficacy, and dosing data to guide their use [41]. This lack of data results in a lack of evidence-based guidelines for the treatment of hypertension in infants, with choice of therapy driven by site experience [6].

Strengths of our study include large sample size and generalizability. This study extracted data from 348 NICUs across the USA and included infants admitted to both academic and community hospitals. However, we did not have access to indications for starting or stopping enalapril

therapy. We also did not have access to dosing data, thus preventing us from determining the relationship between dose or changes in doses and risk of AEs. Certain indications in infants such as hypertension commonly have renovascular etiologies associated with findings of renal insufficiency, resulting in potential for clinical susceptibility bias [7]. Causality between enalapril exposure and AEs cannot be inferred, because these critically ill infants were likely to have other comorbidities that may have contributed to the development of AEs. Given the limitations of our electronic medical record, we were unable to collect data on clinical information including concomitant intravenous fluid composition and thus were unable to control for these other variables that could potentially contribute to the development of AEs.

Falsely elevated potassium levels due to hemolysis of blood samples is a study limitation that cannot be resolved. Information on clinician response to high potassium levels was not available. Even in hyperkalemic subjects with subsequent normal potassium levels, it is unknown whether the normal results were the result of an intervention (e.g., discontinuing potassium-containing fluids) or because the initial sample was hemolyzed. Hyperkalemia is a known AE in adults, with a randomized, double-blind, placebo-controlled clinical trial of 6797 participants demonstrating a higher incidence of hyperkalemia in subjects receiving enalapril compared to placebo (1.2 vs. 0.4%, $p = 0.0002$) [42]. Most cases of enalapril-associated hyperkalemia in adults resolve despite continued therapy [5]. Because of the potential for hemolysis of blood samples, the incidence of hyperkalemia may be overestimated by our study. However, because hyperkalemia is a known AE associated with enalapril use in adults, caution and clinical judgment are advised in the treatment of enalapril-exposed infants with elevated serum potassium measurements.

We observed that, among preterm and term infants without significant structural cardiac disease, hyperkalemia was the most common AE associated with enalapril use. The overall risk for AEs and the risks for hyperkalemia and elevated serum creatinine associated with enalapril exposure are greatest during postnatal ages <30 days and with longer exposures after controlling for gestational age.

Acknowledgements

The Best Pharmaceuticals for Children Act – Pediatric Trials Network Steering Committee Daniel K. Benjamin Jr., MD, PhD, Katherine Y. Berezny, BSMT, MPH, Michael Cohen-Wolkowiez, MD, PhD, Duke Clinical Research Institute, Durham, NC; Gregory L. Kearns, PharmD, PhD, Arkansas Children's Hospital, Little Rock, AR; Matthew M. Laughon, MD, MPH, University of North Carolina, Chapel Hill, NC; Ian M. Paul, MD, MSc, Penn State College of Medicine, Hershey, PA; Michael J. Smith, MD, MSCE, University of Louisville, Louisville, KY; John van den Anker, MD, PhD, George Washington University School of Medicine and Health, Washington, DC; Kelly Wade, MD, Children's Hospital of Philadelphia, Philadelphia, PA.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development David Siegel, MD, Perdita Taylor-Zapata, MD, Anne Zajicek, PharmD, Zhaoxia Ren, MD, PhD, Ekaterini Tsilou, MD, Alice Pagan, BBA.

The EMMES Corporation (Data Coordinating Center) Ravinder Anand, PhD, Traci Clemons, PhD, Gina Simone, BS.

Funding Dr. Ku receives research support from the National Institute of Child Health and Human Development (5T32GM086330-03, 5T32HD043029-13, and 4K12HD043494-14). Dr. Zimmerman receives research support from the Duke Clinical and Translational Science Awards (KL2TR001115-03). Dr. Hornik receives research support for research from the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH) (UL1TR001117). Dr. Smith receives salary support for research from the NIH and the National Center for Advancing Translational Sciences of the NIH (UL1TR001117), the National Institute of Child Health and Human Development (HHSN275201000003I and 1R01-HD081044-01) and the Food and Drug Administration (1R18-FD005292-01); he also receives research support from Cempra Pharmaceuticals (subaward to HHS0100201300009C) and industry for neonatal and pediatric drug development (www.dcri.duke.edu/research/coi.jsp). The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Dr. Benjamin and Dr. Clark have nothing to disclose.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval For this type of study, formal consent is not required. Approval for this study was obtained from the Duke University Institutional Review Board.

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