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

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Background

- Enalapril is used off-label in infants for treatment of hypertension and congestive heart failure
- Safety data in term and preterm infants are lacking
- Previous studies primarily included infants with significant structural heart disease
- Adverse events (AEs) described in previous studies and case reports include acute renal failure and hypotension

Objectives

- Characterize the safety profile of enalapril in term and preterm infants without significant congenital heart disease
- Evaluate risk factors for AEs occurring during enalapril exposure

Methods

- Retrospective cohort study of infants given enalapril in the first 120 days of life and discharged from 348 neonatal intensive care units (NICUs) managed by the Pediatrix Medical Group from 1997-2012
- Excluded infants with significant congenital anomalies
- For infants with multiple courses, only first course examined
- Identified following AEs:
  - Death
  - Hypotension requiring vasopressor therapy
  - Hyperkalemia (> 6 mmol/L)
  - Elevated serum creatinine (≥ 1.3 mg/dL)
- Composite outcome defined as occurrence of ≥1 AE
- AEs attributed to enalapril if occurred on any day of exposure
- Multivariate logistic regression to evaluate these risk factors for AEs:
  - Postnatal age (PNA) on first exposure, exposure duration, gestational age (GA), small for gestational age status (SGA), race, sex, 5-minute Apgar score, and inborn status
- Evaluation of predictors for hyperkalemia, elevated creatinine, and the composite outcome controlled for baseline potassium and creatinine levels using last observed values prior to enalapril exposure

Results

- 662 out of 818,377 infants (0.08%) were exposed to enalapril
- 94% of exposed infants received only 1 course of enalapril
- 106 out of 348 sites (30%) prescribed enalapril at least once

Table 1: Demographics and baseline characteristics (N = 662)

Gestational age, n(%)	
<28 weeks	204 (31)
28–33 weeks	219 (33)
>33 weeks	238 (36)
Birth weight* (g)	1345 (910, 2700)
Male, n (%)	377 (57)
Race/ethnicity, n(%)	
White	308 (47)
Black	109 (16)
Hispanic	187 (28)
Other	28 (4)
Inborn, n (%)	417 (63)
Small for gestational age, n (%)	98 (15)
5-minute Apgar score, n(%)	
0–3	48 (7)
4–6	106 (16)
7–10	477 (72)
Postnatal age at first exposure* (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)
Exposure duration* (days)	3 (1, 8)

*Data presented as median (25th, 75th percentile).

Table 2: Adverse events during exposure (N = 662)

Hyperkalemia	83 (13)
Elevated creatinine	34 (5)
Hypotension	25 (4)
Death	3 (0.5)
Composite outcome	142 (21)

Data presented as n(%).

Table 3: Top 10 concomitant medications (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)

Data presented as n(%).

Figure 1: Enalapril use by site during 1997-2012

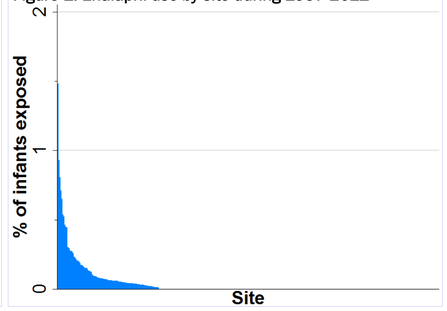

Figure 2: Enalapril use over time

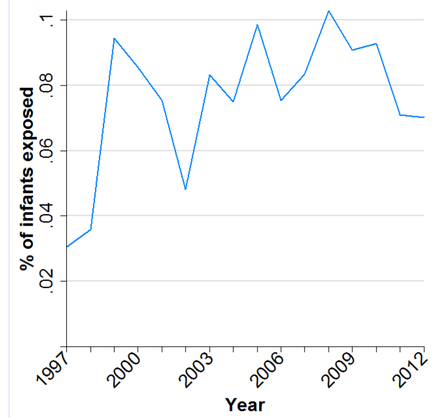

Table 4: Predictors for adverse events during enalapril exposure (N = 662)

	Hyperkalemia	Elevated Creatinine	Hypotension	Death	Composite Outcome
Postnatal age (days)					
<30	**2.47 (1.19–5.12)**	**11.1 (2.72–45.3)**	**15.6 (1.30–189)**	0.35 (0.04–3.31)	**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)	–[a]	2.21 (0.91–5.41)
61–120	Ref	Ref	Ref	–[b]	Ref
Duration of exposure (days)	**1.08 (1.05–1.10)**	1.00 (0.95–1.04)	0.97 (0.92–1.03)	**1.04 (1.02–1.06)**	**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)	–[b]	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)	3.52 (0.19–64.1)	0.87 (0.48–1.60)
>33	Ref	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)	–[b]	1.33 (0.71–2.50)
Race/ethnicity					
White	Ref	Ref	Ref	Ref	Ref
Black	**3.12 (1.51–6.46)**	1.67 (0.53–5.23)	0.24 (0.03–2.04)	–[b]	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)	3.28 (0.51–20.9)	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)	–[b]	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)	0.45 (0.04–4.67)	1.16 (0.72–1.89)
5-minute Apgar score					
0–3	1.59 (0.72–3.52)	1.10 (0.27–4.41)	0.99 (0.18–5.37)	**8.36 (1.44–48.6)**	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)	11.9 (0.58–244)	0.94 (0.46–1.90)
7–10	Ref	Ref	Ref	Ref	Ref
Inborn					
Yes	0.84 (0.46–1.55)	1.03 (0.43–2.47)	0.53 (0.23–1.21)	0.34 (0.02–4.86)	0.76 (0.45–1.26)

Data presented as odds ratio (95% confidence interval).
[a]Only 1 subject first exposed during 30-60 days PNA died; [b]No subjects within these categories died during exposure.

Conclusions

- Enalapril use in the NICU is rare (<1% infants exposed)
- 21% of infants exposed to enalapril suffered ≥1 AE
- Hyperkalemia (13%) and elevated creatinine (5%) were the most common AEs
- First exposure to enalapril during the neonatal period (PNA <30 days) was a significant risk factor for these AEs:
  - Hyperkalemia
  - Elevated creatinine
  - Hypotension requiring vasopressor therapy
  - Composite endpoint
- Exposure duration was a significant risk factor for these AEs:
  - Hyperkalemia
  - Death
  - Composite endpoint

Acknowledgments

This work was funded under NICHD contract HHSN275201000003I for the Pediatric Trials Network.

Dr. Ku receives research support from the National Institute of Child Health and Human Development (5T32GM086330-03 [PIs: Brouwer, Benjamin, Watkins]).

Dr. Benjamin has nothing to disclose.

Dr. Clark has nothing to disclose.

Dr. Hornik receives salary support for research from the National Center for Advancing Translational Sciences of the National Institutes of Health (UL1TR001117).

Dr. Smith receives salary support for research from the National Institutes of Health (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)

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