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Concomitant Ceftriaxone and Intravenous Calcium Therapy in Infants

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OBJECTIVE To determine if increased mortality could be detected with the administration of ceftriaxone and IV calcium in infants through an analysis of a large repository of electronic health records.

METHODS Patients were split into 3 groups: 1) neonates, 2) infants, and 3) infants <1 year whose age was not specified. Deaths were classified into mutually exclusive categories based on the administration and timing of ceftriaxone and IV calcium. Crude death rates were calculated, and logistic regression modeling was used to calculate adjusted relative odds of death with associated covariates.

RESULTS A total of 259,149 infants were identified. Of 79,038 neonates, the proportion of patients that received ceftriaxone and IV calcium within 48 hours who died was 3.8%, compared with 1.95% (IV calcium), 0.3% (ceftriaxone), 1.54% (IV fluids), and 2.03% (parenteral nutrition). For 102,456 infants, the proportions of deaths were 5.47% (ceftriaxone and IV calcium within 48 hours), 0.45% (IV calcium), 0.15% (ceftriaxone), 0.39% (IV fluids), and 5.5% (parenteral nutrition). Multivariate analysis showed increased odds of death in infants who received ceftriaxone and IV calcium within 48 hours, regardless of age, and propensity score–matched analysis showed a more than 2-fold increased risk for death.

CONCLUSIONS The increased risk for death following ceftriaxone and IV calcium administration was noted not only in neonates, but among older infants as well.

ABBREVIATIONS CI, confidence interval; EHR, electronic health record; FDA, US Food and Drug Administration; HIPAA, Health Insurance Portability and Accountability Act; IV, intravenous

KEYWORDS adverse effects; calcium; ceftriaxone; electronic health record; infant; mortality

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Introduction

Ceftriaxone is a broad-spectrum cephalosporin approved for use by the FDA in 1984 and is widely used to treat childhood infections. The primary advantage of ceftriaxone compared with other third-generation cephalosporins is its once-daily dosing, made feasible because of its prolonged half-life and saturable plasma protein-binding characteristics.

The FDA first issued a warning in 2007 regarding an interaction between ceftriaxone and IV calcium-containing products, based on spontaneous reporting of fatal cases in neonates resulting from ceftriaxone-calcium precipitation in the vascular bed of the lungs and kidneys.[1] Although the FDA noted that fatalities had only been reported in neonates, the potential for interaction was present for patients of any age. Upon review of the reported cases, it was determined in most neonates the ceftriaxone/calcium precipitates were due to Y-site incompatibility.[1] The FDA modified its warning in 2009 such that ceftriaxone and calcium-containing products could be sequentially administered in patients older than 28 days provided infusion lines were thoroughly flushed between infusion with a compatible fluid, such as normal saline or 5% dextrose in water.[2] Subsequent studies looking at the administration of ceftriaxone and calcium in adults found no increase for adverse events.[3,4] However, the risk of combined administration has not been assessed in large populations of infants older than 28 days.

The purpose of our study was to evaluate the safety of this potential drug-drug interaction in both neonates ages <28 days and infants ages 29 to 365 days, using a large observational data source covering more than 45 million patients. We investigated the risk of death from concomitant administration of ceftriaxone and calcium in neonates and infants using administration of intravenous fluids without the administration of either drug as the reference group for comparison.

Methods

Data Source and Patient Population. We used CERNER Health Facts (Cerner, Kansas City, MO), a HIPAA-compliant data warehouse of EHRs derived from more than 100 million patients at 600 US health

care centers beginning in the year 2000. We identified all patients ages <1 year who were admitted to the hospital from January 1, 2000, until December 31, 2014, and using text string searches we identified all patients receiving ceftriaxone (Rocephin, Roche, Nutley, NJ) as well as those who received IV calcium-containing products (i.e., calcium chloride, calcium gluconate, Ringer lactate, Plasma-Lyte, Isolyte-R). Separate independent categories of exposure were also created for patients receiving parenteral nutrition products containing calcium (i.e., Calphosan), as well as for patients who received other IV fluid types not containing calcium (such as normal saline products). Using the medication administration record time and date-stamping property of the CERNER Health Facts, we identified patients who received administration of ceftriaxone and calcium-containing products within 48 hours of each other as well as those who received both products concomitantly.

Patients were split into 2 age groups: birth to 28 days (neonates) and 29 to 365 days (infants). Prior to October 2008, only year of age was available within the database; hence, a third group was formed for patients identified as <1 year of age but where the exact age in months or days was not specified. The number of infants, and the number of deaths within the hospital, were classified into: 1) administration of ceftriaxone and calcium-containing products within 48 hours; 2) administration of both products but greater than 48 hours apart; 3) administration of parenteral nutrition; 4) administration of IV calcium alone without ceftriaxone; 5) administration of ceftriaxone without any IV calcium products; 6) administration of parenteral fluids (regardless of ceftriaxone administration); and finally 7) infants receiving only IV fluids without calcium and without receipt of ceftriaxone. This last group served as the reference group for our comparisons. A small number of infants received products from more than 1 category (e.g., receiving both normal saline and lactated ringers, separately, during the course of a hospitalization), and these patients were excluded from the analysis.

For patients who died within 48 hours of receiving ceftriaxone and IV calcium-containing products including parenteral nutrition, we searched for *International Classification of Diseases* (ICD)-9 diagnostic codes that were consistent with the previous reported causes of deaths (518, 518.81, 518.82 acute respiratory failure or pulmonary collapse; 584.X acute kidney failure; and 427.5 cardiac arrest).[5]

Statistical Analysis. All statistical analyses were performed in R version 3.43 (R Code Team, Vienna, Austria) and RStudio version 1.1.383 (R Code Team, Vienna, Austria). Summary statistics included frequencies and percents for demographic variables. Crude death rates were calculated for each exposure category and compared relative to the reference group. Multivariable models were examined by described age category.

Table 1. Demographics (N = 259,149)

Variable	n (%)
Age	
0–28 days	79,038 (30.5)
29–365 days	102,456 (39.5)
Undefined <1 yr	77,655 (30.5)
Race	
African American	66,999 (25.9)
Asian	4181 (1.6)
White	135,133 (52.1)
Hispanic	13,572 (5.2)
Other	39,264 (15.2)
Sex	
Female	112,483 (43.4)
Male	146,570 (56.6)
Unknown	96 (<0.1)

Multivariable logistic regression models adjusted for sex, age, region of the country, and insurance type were used to calculate adjusted relative odds ratios (and their respective 95% CIs) of death associated with main covariates of interest. The group of neonates and infants who received IV fluids was used as the reference category for all analyses. For the category of age <1 year but not further specified, the multivariate logistic model was the same as above except that it was not adjusted for age. All associations were considered significant at the α level of 0.05.

In the largest group of infants, ages 29 to 365 days, we performed a propensity score–matched analysis. Propensity score matching is done to use observational data to closely emulate randomized clinical trials in which clinical equipoise is present, and it addresses the question, as encapsulated by Thomas et al,[6] "What if everyone in the sampled population who could be matched received one treatment or the other treatment?" To accomplish this, we first fit a logistic regression model for the concomitant calcium and ceftriaxone use, using the independent variables of sex, age, region, payer status, and admission diagnoses (78 total categories). We matched calcium-ceftriaxone–exposed infants by propensity score, using the nearest-neighbor method for matching up to 1:4 within strata, to infants in each of the other exposure groups within 10 propensity strata; this process resulted in non-signficant differences in chanracteristics and propensity scores between the groups. We then fit the conditional logistic regression model accounting for matching within strata in order to estimate the relative odds of death as a function of ceftriaxone and calcium administration compared with the reference category.

Results

There were 259,149 neonates and infants ages <1 year. The demographics of this group are shown in

Table 2. Mortality Outcome in Neonates (0 – 28 days) Associated With Ceftriaxone and IV Calcium Administration

Product Administered	Number	Death, n (%)	Odds Ratio* (95% CI)
Ceftriaxone + calcium ≤48 hr	79	3 (3.8)	2.46 (0.77–7.87)
Ceftriaxone + calcium >48 hr	3	1 (33.3)	27.44 (2.47–304.87)
Parenteral nutrition	54,631	1110 (2.0)	1.46 (1.23–1.73)
Calcium alone†	3075	60 (1.9)	1.42 (1.05–1.91)
Ceftriaxone alone	1293	4 (0.3)	0.19 (0.07–0.51)
IV fluids only	17,084	264 (1.5)	Reference

* All odds ratios and CIs adjusted for age, sex, region, and insurance type.
† Excluding parenteral nutrition.

Table 3. Mortality Outcome in Infants Ages 29–365 Days Associated With Ceftriaxone and IV Calcium Administration

Product Administered	Number	Death, n (%)	Odds Ratio* (95% CI)
Ceftriaxone + calcium ≤48 hr	585	32 (5.5)	16.41 (11.11–24.25)
Ceftriaxone + calcium >48 hr	9	0 (—)	0 (0–7.89)
Parenteral nutrition	2079	116 (5.5)	14.83 (11.63–18.91)
Calcium alone†	7474	34 (0.4)	1.52 (1.04–2.21)
Ceftriaxone alone	39,024	60 (0.1)	0.44 (0.32–0.58)
IV fluids only	47,336	188 (0.4)	Reference

* All odds ratios and CIs adjusted for age, sex, region, and insurance type.
† Excluding parenteral nutrition.

Table 1. Of this total, 79,038 neonates were hospitalized between the ages of 0 and 28 days (Table 2). There were 3 deaths (3.8%) among 79 neonates who received ceftriaxone and IV calcium within 48 hours. The administration of ceftriaxone and IV calcium within 48 hours in these 79 neonates occurred after the FDA warning. There was 1 death among 3 neonates who received ceftriaxone and IV calcium in the same hospitalization but separated by at least 48 hours between the end of one product and the start of the other. In comparison, the proportion of deaths was 1.9% among the 3075 neonates who received IV calcium without any administration of ceftriaxone, 0.3% among the 1293 neonates receiving ceftriaxone, and 1.5% among the 17,084 neonates who received only IV fluids and neither IV calcium nor ceftriaxone. There were 54,631 neonates receiving parenteral nutrition, and of these, 2.03% died.

There were 102,456 infants hospitalized between 29 and 365 days, including 585 who received ceftriaxone and IV calcium within 48 hours, and 9 who received ceftriaxone and IV calcium in the same hospitalization but separated by at least 48 hours (Table 3). In these 2 groups, the proportions of deaths were 5.5%, and 0%, respectively. The proportion of deaths was 0.4% among the 7474 infants who received IV calcium without any administration of ceftriaxone, 0.1% among the 39,024 infants receiving ceftriaxone, and 0.4% among the 47,336 infants who received only IV fluids and neither IV calcium nor ceftriaxone. There were 2079 infants who received parenteral nutrition alone, and of these, 5.5% died.

Finally, there were 77,655 infants ages <1 year (but without exact age specified; Table 4). Of these, 467 received ceftriaxone and IV calcium within 48 hours, and 67 received ceftriaxone and IV calcium in the same hospitalization but separated by at least 48 hours; the proportions of deaths were 4.5%, and 3.0%, respectively. The proportion of deaths was 0.2% among the 2779 patients receiving IV calcium without ceftriaxone, 0.08% among the 23,299 patients receiving ceftriaxone, and 0.6% among the 24,724 patients who received only IV fluids and neither IV calcium nor ceftriaxone. There were 24,063 patients receiving parenteral nutrition, and of these, 2.4% died.

There were 3 deaths in neonates, 32 deaths in infants, and 21 deaths in infants (age not specified) with overlapping or with 48-hour administration of ceftriaxone and IV calcium or parenteral nutrition fluids. Multivariate analyses showed increases in the odds

Table 4. Mortality Outcome in Infants Undefined <1 Year Associated With Ceftriaxone and IV Calcium Administration (Before October 2008)

Product Administered	Number	Death, n (%)	Odds Ratio* (95% CI)
Ceftriaxone + calcium ≤48 hr	516	22 (4.3)	8.47 (5.35–13.41)
Ceftriaxone + calcium >48 hr	18	1 (5.5)	10.15 (1.32–76.33)
Parenteral nutrition	24,063	575 (2.4)	4.49 (3.73–5.4)
Calcium alone†	2779	6 (0.2)	1.1 (0.65–1.85)
Ceftriaxone alone	23,299	18 (0.08)	0.14 (0.09–0.23)
IV fluids only	24,724	143 (0.6)	Reference

* All odds ratios and CIs adjusted for age, sex, region, and insurance type.
† Excluding parenteral nutrition.

Table 5. Propensity Score Adjusted Mortality Outcome in Infants Ages 29–365 Days Associated With Ceftriaxone and IV Calcium Administration*

Product Administered	Number	Death, n (%)	Odds Ratio† (95% CI)
Ceftriaxone + calcium–containing products	589	32 (5.43)	2.9 (1.67–5.04)
Parenteral nutrition	199	16 (8.04)	2.18 (1.1–4.32)
Ceftriaxone alone	858	7 (0.81)	0.41 (0.16–1.03)
IV fluids only	1059	25 (2.36)	Reference

* Odds ratio for administration of IV calcium alone not included because of small sample size and instability of estimate
† All odds ratios and CIs adjusted for age, sex, region, and insurance type.

ratios for ceftriaxone and IV calcium administered to neonates, ranging from 2.46 (95% CI, 0.77–7.87) for products administered within 48 hours of each other, to 27.44 (95% CI, 2.47–304.87) for neonates who received both products within the same hospitalization but separated by more than 48 hours (Table 2). Increased risks were also found for infants 29 to 365 days, with odds ratios of 16.41 (95% CI, 11.11–24.25) for those receiving both ceftriaxone and IV calcium within 48 hours of each other (Table 3). Among children ages <1 year, the odds ratios were 8.47 (95% CI, 5.35–13.41) and 10.03 (95% CI, 1.32–76.33) for infants who received ceftriaxone and IV calcium within 48 hours of each other or greater than 48 hours, repectively (Table 4). It is important to note that these calculations were based on a small numbers of deaths, with the resultant wide CIs.

The propensity score–matched conditional logistic regression analysis was performed to further evaluate the risk of ceftriaxone and IV calcium administered to infants ages 29 to 365 days. In this analysis, there were a total of 589 infants who received ceftriaxone and IV calcium who were propensity score–matched to a total of 2253 infants. Among the exposed infants, the odds of death remained elevated and were 2.9-fold (95% CI, 1.67–5.04) higher compared with the reference group (Table 5). The Supplemental Table summarizes the timing of ceftriaxone and calcium administration relative to the time of death as well as the diagnoses likely associated with death, highlighting the ICD-9 diagnoses that may be associated with precipitation of calcium and ceftriaxone in the lungs and kidneys.

Discussion

In this study of almost 250,000 neonates and infants ages <1 year, we found that ceftriaxone and IV calcium administered either concomitantly, within 48 hours of each other, or separated by more than 48 hours but during the same hospital admission increased risks of death. This risk of death was not only among neonates ages <28 days but also among infants ages 29 to 365 days. The Supplemental Table summarizes the timing of death relative to ceftriaxone and calcium administration and provides ICD-9 diagnoses most likely associated with death, highlighting diagnoses associated with possible precipitation in the vascular bed of the lungs and kidneys. Our findings add to the current state of evidence about the safety profile of these 2 products when they are administered in close temporal proximity to each other. Our results suggests that the previously identified risk among neonates is observable within this hospitalized cohort of neonates ages <28 days, and that this increased risk is also identifiable among infants who are older than 1 month.

Ceftriaxone is a broad-spectrum "third-generation" cephalosporin, and its once-daily dosing made it a very

popular choice to treat childhood infections. One third to two thirds of the drug is eliminated by renal excretion, and the remainder via the biliary system. Ceftriaxone reaches biliary and urine concentrations 20 to 150 times higher than in plasma and can form insoluble calcium salts, leading to renal and biliary lithiasis.[7-10] An FDA warning in 2007 regarding the interaction of ceftriaxone and IV calcium-containing products was based on spontaneous reporting of fatal cases in neonates complicated by ceftriaxone-calcium precipitation in the pulmonary and renal vascular beds.[2] Although the FDA noted that fatalities had only been reported in neonates, the potential for interaction, was present for infants of any age. The FDA warning was based on the deaths of 7 of 8 neonates and infants who received both ceftriaxone and calcium. A ninth neonate was included in the original FDA warning, but an autopsy later determined that this infant died of pneumonia and sepsis.[1] Based on the half-life of ceftriaxone, the FDA recommended that patients not receive ceftriaxone and calcium containing products within 48 hours of each other.

After it was determined that in most neonates the ceftriaxone/calcium precipitates were due to Y-site incompatibility, the manufacturer at the request of the FDA conducted *in vitro* studies in the plasma of adults and neonates to assess the potential for precipitation at varying ceftriaxone and calcium concentrations, including concentrations greater than what would be expected *in vivo*. No correlation was found between the potential for precipitation and the concentrations of ceftriaxone and calcium; another *in vitro* study confirmed these results.[11] Subsequently the FDA modified its warning in 2009 such that ceftriaxone and calcium-containing products could be sequentially administered in patients older than 28 days provided the infusion lines are thoroughly flushed between infusion with a compatible fluid.[2] Although the administration of ceftriaxone and calcium in adults has not been associated with an increased risk of adverse events, the risk of joint administration had not been assessed until now in a large cohort of hospitalized children younger than 1 year.[3,4] Our findings suggest that the risk for adverse events after coadministration exists not only in neonates ages ≤28 days but may also exist in infants between 1 month and 1 year of life.

The strengths of this study include the use of a large database derived from EHRs from health systems around the United States, enabling us to evaluate risks at different ages. This approach has been recommended by the National Academy of Medicine to detect adverse drug events in hospital patients to study the occurrence of harm to patients.[12] These data were likely free of bias because exposure to IV fluid type and to ceftriaxone was recorded as part of routine medical care and prior to the outcome of interest. In addition, we were able to adjust for common covariates, such as sex, region of the country, and insurance status, which might have otherwise served as potential confounders. In addition, the detailed data allowed propensity score matching to further evaluate the risk of ceftriaxone and IV calcium administered to infants older than 29 days. In this analysis, the risk was markedly lowered compared with the multivariate analysis (with the odds ratio decreasing from 16.41 to 2.9), but it remained statistically elevated.

Limitations of the study were that we were unable to review the original medical records to directly confirm either the exposure or the outcome. Additionally, because of a limitation in the way some age data were recorded, for a significant number of children we could not estimate age any more precisely than being <1 year. We analyzed this group separately, and in fact, the results of that analysis appear to be intermediate between the findings of the neonates ages ≤28 days and that of the infants ages 29 days to 365 days. Lastly, some of the categories had a small number of deaths, resulting in increased variablity and risk estimates with wide CIs. For these groups, the results should be interpreted cautiously.

As expected, the baseline mortality was higher for infants in any group who received parenteral nutrition, reflecting the fragile underlying health status of this particular group. An unexpected finding from our study was the higher mortality experienced by children receiving calcium-containing IV fluids (such as lactated ringers) compared with children receiving non–calcium-containing saline IV fluids. We have no ready explanation for these findings, but given the widespread use of both these IV fluids in hospitals around the country, further research is needed.

Conclusion

Ceftriaxone and IV calcium administered either concurrently, within 48 hours of each other, or separated by more than 48 hours was associated with an increased risk of death among neonates ages <29 days as well as among infants ages 29 to 365 days and infants <1 year where the age was not specified. The previous risk among neonates is supported with this hospitalized large cohort of neonates and infants, but there was also an identifiable risk among infants older than 1 month.

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