Evaluation of a Potential Clinical Interaction between Ceftriaxone and Calcium[▽]

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In April 2009, the FDA retracted a warning asserting that ceftriaxone and intravenous calcium products should not be coadministered to any patient to prevent precipitation events leading to end-organ damage. Following that announcement, we sought to evaluate if the retraction was justified. A search of the FDA Adverse Event Reporting System was conducted to identify any ceftriaxone-calcium interactions that resulted in serious adverse drug events. Ceftazidime-calcium was used as a comparator agent. One hundred four events with ceftriaxone-calcium and 99 events with ceftazidime-calcium were identified. Adverse drug events were recorded according to the listed description of drug involvement (primary or secondary suspect) and were interpreted as probable, possible, unlikely, or unrelated. For ceftriaxone-calcium-related adverse events, 7.7% and 20.2% of the events were classified as probable and possible for embolism, respectively. Ceftazidime-calcium resulted in fewer probable embolic events (4%) but more possible embolic events (30.3%). Among cases that considered ceftriaxone or ceftazidime and calcium as the primary or secondary drug, one case was classified as a probable embolic event. That patient received ceftriaxone-calcium and died, although an attribution of causality was not possible. Our analysis suggests a lack of support for the occurrence of ceftriaxone-calcium precipitation events in adults. The results of the current analysis reinforce the revised FDA recommendations suggesting that patients >28 days old may receive ceftriaxone and calcium sequentially and provide a transparent and reproducible methodology for such evaluations.

Ceftriaxone (CRO), an expanded-spectrum cephalosporin approved for use by the United States Food and Drug Administration (FDA) in 1984 (29), has a wide range of antimicrobial activity and is currently recommended in the national guidelines for the treatment of many community-acquired infections, including pneumonia and meningitis (12, 13). In September 2007, the FDA issued an Alert to Healthcare Professionals to revise the U.S. package labeling due to concerns of adverse events (28). Specifically, the warning suggested that CRO and calcium-containing products should not be coadministered to any patient receiving either agent within the previous 48 h in order to prevent possible end-organ damage secondary to CRO-calcium precipitation. The FDA warnings were provoked by a report of fatal outcomes in neonates, in whose lungs and kidneys CRO-calcium precipitates were discovered (1). However, the majority of these outcomes were due to a Y-site incompatibility between CRO and calcium administered simultaneously through the same intravenous

line (28). After a recent analysis of two *in vitro* studies with neonatal and adult plasma found no direct correlation between the potential for a precipitation reaction with various concentrations of CRO and calcium, the FDA modified its warning on 14 April 2009 to recommend that CRO and calcium-containing products may be sequentially administered in patients older than 28 days if the infusion lines are thoroughly flushed between infusions with a compatible fluid (24, 28). Such recommendations are now in line with those of the French Health Products Safety Agency (AFSSAPS) and the World Health Organization (WHO), which have warned against using CRO and calcium simultaneously in infants, in whom the adverse event has been documented; however, neither agency has offered formal recommendations regarding the usage of CRO and calcium in adults (2), probably due to the lack of CRO-associated end-organ toxicities caused by calcium-containing precipitates in adults.

As CRO is widely used in the United States to treat numerous invasive bacterial infections, several authors took interest in the initial FDA safety warning (10, 22, 23). Since recent changes have been implemented in the United States on the basis of data from *in vitro* studies, vigilant safety monitoring and clinical analysis can provide the best guidance for the use of these agents. Hence, we reviewed the available medical

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literature for reports of CRO-calcium precipitation in adults and analyzed the FDA MedWatch Adverse Event Reporting System (AERS) databases for adverse drug interactions reported with CRO treatment in association with calcium. For comparison, we also searched AERS for interactions reported between ceftazidime (CAZ) and calcium.

MATERIALS AND METHODS

Review of the published literature. A literature review was conducted in an attempt to identify CRO-calcium interactions that resulted in a serious adverse drug event (ADE) in adults. We reviewed the data available in the public domain by searching Medline via the PubMed search engine. MeSH search terms were used for all literature inquiries. The term “ceftriaxone,” “calcium,” or “adverse events” was combined with the Boolean combiner “AND” in order to match with the following outcomes: “embolism” or “precipitation.” Full manuscripts were obtained for all publications that met the inclusion criteria. Manuscripts written in all languages were considered. The references cited in those publications were reviewed for relevance and were obtained when applicable.

Adverse Event Reporting System database. FDA’s AERS database was analyzed by using preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA), and the time period from 1998 through the second quarter of 2007 was targeted. We chose to use data beginning in 1998 due to the FDA’s implementation of the AERS database that year, which provided better consistency in data content and structure. The data extended through the second quarter of 2007 because that was the last data set available for public use when we analyzed the AERS data. We identified all ADEs reported in the AERS in which CRO and calcium or CAZ and calcium were reported in any role (suspect or concomitant). Age, gender, and event date were used to identify and remove duplicative reports. The following variables were summarized for all AERS cases evaluated: preferred MedDRA term, patient age, patient sex, the year of the report, the reporter’s occupation, the indication for antibiotic treatment, patient outcome, and the source of the report. The drugs (CAZ, CRO, and calcium) were categorized according to the reporter’s attribution of causality as primary suspect, secondary suspect, or concomitant. As reporters could select from any of the choices, it was assumed that these classifications represented a gradient in the continuum of the likelihood of drug involvement. Patient outcomes were classified according to exact AERS reporting terms of death, disabling, hospitalization, life threatening, required intervention, or other. Sources comprising company representatives, health professionals, literature report, foreign study, or other were reported. Complete data were not available for all cases, and all percentages are based on the available data. To examine the overall clinical course of each case and avoid double reporting, we linked follow-up reports back to the original reports.

Adverse drug event classification. ADEs were assessed for the possibility that the embolic event caused pulmonary or renal failure. ADEs were classified according to the National Cancer Institute Cancer Therapy Program Evaluation: Common Terminology Criteria for Adverse Events (version 3.0; CTCAE) attribution standards: unrelated, unlikely, possible, or probable (19). Definitions were adapted and utilized as follows: “unrelated” was no renal or pulmonary involvement. “Unlikely” was renal or pulmonary involvement, but no clear relationship to embolic event was evident (e.g., multisystem organ failure or events that are likely not to be due to end-organ damage caused by embolic events, such as with prerenal disease). “Possible” was renal or pulmonary involvement that could be related to an embolic event. “Probable” was renal or pulmonary involvement that could be related to an embolic event and reporter suggestion of CRO or CAZ as a primary or secondary drug in combination with calcium as a primary, secondary, or concomitant drug.

Two authors (M.H.S. and J.S.E.) independently reviewed and classified all ADEs for the potential of an embolic event causing end-organ failure (renal or pulmonary failure). Disagreements in classification between the two reviewers were settled by a third reviewer (M.P.). Majority rule was used for discrepancies in classification.

Data analysis and statistical evaluation. Descriptive statistics were calculated for all study variables. These included the number (*n*), the mean, the standard deviation for interval measures, and *n* and percent for categorical measures. Bivariate statistical comparisons between patient groups, defined by taking CRO versus CAZ, were performed by using optimal discriminant analysis (ODA), an exact nonparametric method that is isomorphic with Fisher’s exact test for binary data and that identifies the threshold value which specifically maximizes intergroup discrimination for ordinal values (32). A multivariable model for discriminating these patient groups was obtained by using hierarchically optimal classi-

TABLE 1. Demographics

Variable	Value for:	
	CRO (<i>n</i> = 104)	CAZ (<i>n</i> = 99)
Mean (SD) age (yr)	58.6 (19.3) ^a	45.8 (24.7) ^b
No. (%) male	64 (62.7) ^c	56 (57.1) ^d
No. (%) of cases with the following report source:		
Health professional	50 (48.1)	54 (54.5)
Distributor	1 (1.0)	0 (0.0)
Company representative	3 (2.3)	4 (4.0)
General source, manufacturer	1 (1.0)	18 (18.2)
General source, other	0 (0.0)	1 (1.0)
Literature	7 (6.7)	6 (6.1)
Consumer	2 (1.9)	5 (5.1)
Foreign	29 (27.9)	41 (41.4)
Study	12 (11.5)	26 (26.3)
Other	22 (21.2)	18 (18.2)

^a *n* = 91.

^b *n* = 85.

^c *n* = 102.

^d *n* = 98.

fication tree analysis, an exact nonparametric method that involves chained ODAs and that explicitly maximizes model accuracy in predicting class membership status (31, 32).

RESULTS

Published literature. With the exception of biliary sludging (27) and one case of nephrolithiasis (11), we found no reports in the primary literature of possible CRO-calcium precipitation or embolic events that resulted in end-organ dysfunction in adults.

Adverse Event Reporting System database. Two hundred three total individual safety reports were identified and evaluated for the occurrence of possible embolism among persons who received CRO plus calcium or CAZ plus calcium (Table 1). CRO plus calcium was listed as having been received in 104 cases (51%), and CAZ plus calcium was listed as having been received in 99 cases (49%). Patients ranged in age from newborn to 94 years. Twenty-two cases involved individuals under the age of 18 years. The patients were less than 1 year old in five of these cases. Twenty of the 22 individuals under 18 years of age had received CAZ. Among all patients, the patients who had received CAZ had fewer probable embolic events (4%) but more possible embolic events (30.3%) than the patients who received CRO, among whom 7.7% of the events were classified as probable for embolism, while 20.2% of the events were classified as possible. A total of 18/203 (8.9%) events were reported with either drug as the primary or the secondary agent in conjunction with calcium as a primary or a secondary agent (14 events involving CRO versus 4 events involving CAZ) (Table 2). Two events occurred in the group that received CRO plus calcium and were classified as probable embolic events; one patient ultimately died, although a definitive assessment of causality was not possible with the limitations of the data sources. The occurrence of the preferred MedDRA terms is located in Table 3. Additional cases (*n* = 48) listed CRO (*n* = 24) or CAZ (*n* = 24) as the primary or secondary drug and calcium as a concomitant therapy. Of these, six CRO

TABLE 2. Assessment of relationship likelihood and patient outcomes

Outcome	No. (%) of patients treated with:	
	CRO	CAZ
Cases involving an embolic event		
Probable event	8 (7.7)	4 (4.0)
Possible event	14 (13.5)	27 (27.3)
Possible, nonrenal, nonpulmonary event	7 (6.7)	3 (3.0)
Unlikely	0 (0)	10 (10.1)
Unrelated	75 (72.1)	55 (55.6)
Reporter attribution	14 (13.5)	19 (19.2)
Primary cause by drug		
Secondary cause by drug	24 (23.1)	9 (9.1)
Concomitant cause by drug	68 (65.3)	71 (71.7)
Primary cause by calcium	2 (1.9)	2 (2.0)
Secondary cause by calcium	15 (14.4)	4 (4.0)
Concomitant cause by calcium	88 (84.6)	94 (94.9)
Primary or secondary cause by both drug and calcium	14 (13.5)	4 (4.0)
Concomitant drug and calcium	24 (23.1)	24 (24.2)
Patient ultimate disposition with ADE	34 (32.7)	41 (41.4)
Death		
Disabling	1 (1.0)	4 (4.0)
Life threatening	16 (15.4)	33 (33.3)
Death, disabling, or life threatening	51 (49.0)	77 (77.8)
Required intervention	18 (17.3)	9 (9.1)
Hospitalization	45 (43.3)	45 (45.5)
Reaction treated with drug ^a	0 (0.0)	4 (4.0)
Patient recovered ^a	0 (0.0)	5 (5.1)
Nonserious ^a	0 (0.0)	1 (1.0)
Other	41 (39.4)	18 (18.2)

^a Data were gathered prior to 1998.

cases and four CAZ cases were classified as probable embolic events. Four of the six CRO-treated patients died, whereas none of the CAZ-treated patients died.

Bivariate statistical analysis revealed two statistically reliable effects. First, the patients in the group treated with CRO were older ($P < 0.005$). While the difference was statistically reliable, the associated ESS—a standardized index of classification accuracy in which 0 is chance accuracy and 100 is perfect accuracy—was 25%, reflecting moderate ecological validity (31, 32). Second, the CRO-treated patients had fewer life-threatening experiences ($P < 0.004$), with the ESS being 18%, indicating relatively weak ecological validity. Jackknife validity analysis revealed that both effects are likely to cross-generalize to an independent random patient sample (32). Other bivariate findings were generally equivocal. Classification tree analysis additionally identified that among those patients experiencing any event (death, disabling, or life-threatening events), more patients receiving CRO (25/28, 89.3%) than patients receiving CAZ (21/35, 60%) died ($P < 0.02$; ESS = 42%, indicating a moderate effect). When the sample was restricted to patients having a probable or a possible renal or pulmonary event, Classification tree analysis was unproductive due to an insufficient statistical power attributable to the small number of patients experiencing probable or possible renal or pulmonary events.

TABLE 3. Classification of reported ADEs by drug group and consensus renal/pulmonary/other embolic phenomena

Clinical phenomenon	No. of patients treated with:	
	CRO	CAZ
Probable embolic event		
Apnea	0	1
Dialysis	1	0
Pleural effusion	1	0
Pulmonary embolism	4	0
Renal failure	4	0
Renal impairment	1	1
Respiratory arrest	1	0
Respiratory disorder	0	1
Respiratory failure	1	0
Possible embolic event		
Acute respiratory distress syndrome	3	0
Apnea	0	1
Increased blood creatinine level	1	0
Dyspnea	2	0
Hypoxia	0	1
Lung infiltration	0	1
Nephropathy	0	1
Decreased oxygen saturation	0	1
Pleural effusion	2	4
Pulmonary embolism	2	0
Pulmonary hemorrhage	0	2
Pulmonary edema	0	2
Renal disorder	0	1
Renal failure	5	11
Respiratory arrest	0	2
Respiratory disorder	1	0
Respiratory distress	1	0
Respiratory failure	1	3
Tachypnea	0	2
Possible nonrenal, nonpulmonary, embolic event		
CVA ^a	2	0
Disseminated intravascular coagulation	2	3
DVT ^b	1	0
Dyspnea	1	0
Hypoxia	1	1
Pleural effusion	1	1
Renal failure	2	0
Thromboembolism	1	0
Thrombotic microangiopathy	1	0

^a CVA, cerebrovascular accident.^b DVT, deep vein thrombosis.

DISCUSSION

We found occasional occurrences of possible or probable embolic events reported after treatment with either CRO or CAZ and calcium, likely indicating similar probabilities of embolic events between the drugs. Our assessment was completed by using a compilation of ADE reports for two similar expanded-spectrum cephalosporins and concomitant calcium administration. In fact, we found only 16 incidents in which we deemed the event to be probably due to a drug interaction (Table 3). This number is larger than that reported in Table 2, as some cases involved multiple events. Furthermore, the number of cases in which an adverse drug event was probably or possibly related to the use of a drug in combination with calcium was roughly evenly divided between those receiving CRO ($n = 43$)

TABLE 4. Summary of results by French Commission of Pharmacovigilance on possibility of reaction of CRO and calcium^a

Data source	No. of patients									
	Less than 2 yr old					Greater than 2 yr old				
	Renal event	Pulmonary event	Biliary event	Other	Death	Renal event	Pulmonary event	Biliary event	Other	Death
Regional	2	0	0	4	1	2	0	3	0	0
International	1	0	1	2	0	3	0	14	0	0
Supplemental	7	0	13	9	2	0	0	0	0	0

^a Data are from reference 1.

and those receiving CAZ ($n = 40$) (Table 3). Once again, this number is higher than that reported in Table 2, for the same reason noted above. The relatively similar numbers of ADEs are important, as there is no current concern for a precipitation reaction between CAZ and calcium. Even our probable events are likely overcalls, as alternative hypotheses for pulmonary and renal failure exist (e.g., acute interstitial nephritis with expanded-spectrum cephalosporins), even in the presence of calcium. We found that when patients experienced dire outcomes (death or disabling or life-threatening conditions), more patients in the CRO group died ($P < 0.02$); however, when the analysis was restricted to the more applicable data (only those with a probable or a possible renal or pulmonary event), the sample was too small—and the effects were too weak—to support a productive multivariable analysis. Thus, our results suggest a low to no incidence of CRO-calcium embolic events leading to end-organ toxicity in adults.

Others have also recently analyzed the AERS database and focused specifically on the neonatal population (8). A total of seven cases were identified among the individuals in this cohort, six of which resulted in death. The neonates were 3 weeks of age or younger in five of these six cases; age was not recorded in the sixth report. Many of the neonates received doses of CRO higher than those recommended in the package insert, and some of the neonates received the drug via intravenous push administration, which is not recommended due to the increased initial serum concentrations that result. Additionally, none of the seven cases occurred in the United States (8). This analysis supports the FDA warning that CRO not be used by neonates (≤ 28 days of age) if they are receiving (or are expected to receive) calcium-containing intravenous products.

The history of the events leading to the multiple warnings is complex and can be difficult to follow. The 2007 warning issued by the FDA emanated from a report generated by the French National Commission of Pharmacovigilance on 31 January 2006 (1) which detailed fatal outcomes in neonates as a result of CRO-calcium precipitates in the lungs and kidneys. The investigation was conducted between 2002 and 2004 by the Regional Center of Pharmacovigilance (Paris, France) and combined international laboratory data with regional French data (Table 4) (1). Ten of 77 regional files and 21 of 247 international files were selected for in-depth reviews. Within the 10 regional files, one calcium-CRO interaction resulting in death occurred in a premature infant in 2002. In 2004, one “favorable outcome” occurred. This outcome was not further defined, but one can speculate that the patient survived. Additionally, there was suspicion of one CRO-acetaminophen and calcium gluconate interaction (outcome undefined), one

error of administration, and seven cases of lithiasis in six total patients (two renal events in infants and one in a child, two biliary events in children, and one case of mixed lithiasis). Within the chosen international reports, newborn reactions included one case of renal lithiasis, one case of biliary lithiasis, and two suspected cases of undetermined lithiasis. In the 2- to 18-year-old segment, there were 13 cases of biliary lithiasis, 2 cases of renal lithiasis, and 2 cases of mixed lithiasis. After the completion of this initial inquiry, the investigators reviewed 178 additional international cases dating from 1996 to 2001 in children less than 2 years of age. These data revealed 7 cases of calcium-CRO interactions, 13 cases of biliary lithiasis, and 7 cases of renal lithiasis (14 of these cases occurred in infants less than 1 year old, and 8 of these cases were less than 6 months), as well as 2 deaths due to unknown causes. Of all the lithiasis reviewed by the commission, approximately 75% of the total cases occurred in children less than 18 years of age (1). The FDA later stated that it had uncovered three additional fatalities in neonates and concluded that it was necessary to institute a modification to the labeling of CRO (28). While the exact sources were unclear, the FDA cited a total of nine cases, including eight deaths. In five cases, embolic events appeared to lead to patient demise, with crystalline structures being identified in three of the cases. In one of these cases, crystalline emboli were found in both the lungs and the kidneys. The remaining three cases died as a result of unclear causes (18).

Internationally, the events triggered heterogeneity in guidance. The AFSSAPS and the WHO issued warnings asking providers to refrain from using CRO and calcium simultaneously in infants, although neither agency has offered formal recommendations regarding their usage in adults. In a November 2006 release, the AFSSAPS indicated that CRO was contraindicated in premature infants up to 41 weeks of age and in term neonates less than age 28 days with hyperbilirubinemia or concomitant calcium use. Likewise, the latest WHO recommendations mirror the French recommendations (2) (Table 5). Thus, the majority of recommendations are now focused on neonates.

The lack of documented clinical events in adults is supported by the results of *in vitro* experiments and calculations. An *in vitro* study completed by Roche and the FDA in 2009 evaluated the recovery of CRO (i.e., the purported precipitation) in pooled human plasma according to various concentrations of calcium and CRO (7). Purported precipitation occurred at lower calcium concentrations for isomorphous CRO concentrations in neonatal plasma than in adult plasma (precipitation likely at ≥ 16 mg/dl and ≥ 24 mg/dl, respectively). Such results indicate that there may be differences in the level of protein

TABLE 5. Recommendations by governing bodies

Governing body (reference)	Description of guidelines
FDA (28)	In 2007, CRO should not be administered within 48 h of administration of calcium-containing products for any patient; in 2009, CRO and calcium-containing products may be sequentially administered if the infusion lines are thoroughly flushed between infusions with a compatible fluid for patients greater than 28 days of age
WHO (2).....	Not for use by premature infants until 41 wk of age (gestational age at delivery plus wk after birth); consider restriction below 1 mo of age since in several situations it is contraindicated in this age group and other alternatives are available
AFSSAPS (1).....	CRO is contraindicated in premature infants until 41 wk of age (gestational age at delivery plus wk after birth) and in term neonates less than 28 days of age if there is hyperbilirubinemia or if the neonate is receiving calcium

binding which exacerbate precipitation. One can also consider the likelihood of precipitation on the basis of the known serum concentrations of CRO and calcium (Table 6). To estimate calcium serum concentrations conservatively, a well-stirred model, as well as zero-order infusion and no distribution (the total volume is equal to the intravascular volume), was assumed for calcium. Dose calculations for calcium were based on mg/kg dosing (16) and average weights for age stratifications for each age group (20). Free calcium concentrations were used for the calculations (27). The maximal expected CRO concentrations were obtained from values in the literature (17, 24, 26). Calculation of the saturation index was based on the product of the maximal expected serum CRO concentration obtained at steady state (post-distributive phase) and maximal free calcium concentration (the supraphysiologic concentration plus the bolus dose concentration) divided by the solubility product constant (27). Analysis of these age-stratified saturation indices reveals that neonates have a saturation index twofold greater than that for adults (Table 6). The calculations showing a higher saturation index for neonates as a result of higher calcium concentrations coupled with the *in vitro* findings that precipitation occurs at calcium concentrations ≥ 16 mg/dl for neonates and ≥ 24 mg/dl for nonneonates suggests that neonates are at the highest risk for precipitation. The findings empirically support the presence of CRO-calcium precipitation when conditions are favorable for this outcome and, hence, support the current FDA contraindication of CRO and calcium in patients less than 28 days old (24, 28). Additionally, these data support the retraction of the 2007 FDA warning (that all age groups not receive CRO and calcium-containing products within 48 h of one another) (28). One should also consider that certain variables can make precipitation more favorable. Pathophysiology, such as dehydration, may dispro-

portionately increase drug and calcium concentrations and may place neonates at increased risk for precipitation compared to the risk for adults when they are given CRO and calcium in combination.

The findings of *in vivo* studies with animals should also be considered. Supplementary investigations with animals have provided evidence of precipitation of the calcium salt of CRO in the gallbladder bile of dogs and baboons; however, the likelihood of this occurrence in humans is thought to be lower since CRO in humans has a prolonged half-life compared to that in the animals studied, the calcium salt of CRO is more soluble in human bile, and the calcium concentrations in humans are reduced (24). While the likelihood of precipitation is lower for humans, the potential for manifestation is not zero and may be higher in certain scenarios. For example, the collecting tubules of organs that typically function in the clearance of xenobiotics may experience elevated drug concentrations. Thus, it is not surprising to observe biliary sludging or nephrolithiasis in patients who receive CRO and calcium, as high concentrations predispose individuals to these conditions (4, 18, 27). In the biliary tract, CRO concentrations are elevated due to biliary excretion (40% of total elimination); the concentrations of CRO can exceed the concentrations measured in serum by 20 to 150 times (6, 27). Additionally, when CRO is secreted into bile, a passive flow of calcium ions is induced (30). In both children and adults, precipitation events are most often transient and the incidence of lithiasis is $<0.1\%$ (15). Such events may be more common and predictable in individuals with high concentrations of CRO in the gallbladder due to fasting or dehydration, as is common in elderly individuals or individuals with impaired gallbladder emptying (14, 27).

While this phenomenon is predictable in the gallbladder, precipitation has occurred in the kidneys and lungs of neonates

TABLE 6. Calculation of saturation indices

Age group	Assumed wt (kg) (20)	Maximum elemental calcium dose recommended (16)	Avg intravascular vol (ml/kg) (3)	Expected maximum calcium concn after bolus injection (mg/liter) ^a	Expected physiologic free calcium concn (mg/liter)	Expected CRO maximum concn ($\mu\text{g/ml}$) ^b (17, 24, 26)	CRO/calcium product (mol/liter ²)	CRO/calcium saturation index
Neonates	3.6	37.5 mg/kg	80	469	38	173	2.12×10^{-6}	1.31
Infants	6.0	16.25 mg/kg	80	203	45	200	1.32×10^{-6}	0.82
Children	12.6	16.25 mg/kg	75	217	44	151	1.04×10^{-6}	0.64
Adults	70	500 mg per dose	70	102	44	257	1.10×10^{-6}	0.68

^a Expected calcium concentration assuming the use of a bolus dose of calcium and a well-stirred model with zero-order infusion. The total volume is equal to the intravascular volume (no distribution).

^b CRO doses and concentrations assuming the most aggressive FDA-approved dosing.

as embolic phenomena from the circulating blood supply (1, 10, 18, 28). These events might be explained by the possibility that neonates metabolize CRO differently than adults, since their biliary secretion pathway is poorly developed, resulting in elevated serum concentrations (25, 27). A lower total systemic clearance produces a 100 to 200% longer half-life in infants than in children and adults (25). Similar precipitation events could potentially occur in adults, as there are many clinical scenarios that result in simultaneously high concentrations of endogenous calcium and administered CRO, such as treatment for superimposed infections in dehydrated adult patients with elevated serum calcium concentrations. We suggest the use of caution when the use of sequential therapy is contemplated in these scenarios and agree with the labeling that suggests that intravenous therapy with CRO and calcium not be commenced simultaneously in any patient (9, 24). Thus, *in vitro* studies, a systematic analysis of an adverse event reporting database, and the lack of clinical observations of adverse events yielding similar results for CRO and CAZ agree that precipitation events leading to renal or pulmonary compromise are not likely for most adult patients.

To our knowledge, this study employs the most comprehensive clinical evaluation to date of a possible reaction between CRO and calcium in patients, although several important limitations exist. First, our study is restricted to reported data available from the public domain and MedWatch reports. While all medications prescribed in the United States are subject to MedWatch reporting, AERS data represent reports that are voluntary, sporadic, and often incomplete (5). Differences in the numbers of reports between drugs relate to utilization rates as well as many other notable limitations. To retain high sensitivity, we included all reports of CRO or CAZ in conjunction with calcium for any adverse drug event reported to MedWatch. Second, CAZ was used as a comparator of the associated but likely noncausal precipitation events. While these methods are nonspecific for the identification of embolic events, the “noise” created by this mechanism of study is high in the CAZ group, which signifies that most reactions observed are probably unrelated to the administration of the drugs in combination with calcium; this is further emphasized by the fact that older patients were identified in the CRO-treated group. Since neonates appear to be the only category of patients with an embolic event relationship to date, a study mechanism with low levels of noise should have identified CRO-treated patients as younger. Our model lost the ability to predict outcomes when we restricted the data to those patients whom we classified as probable or possible renal or pulmonary events, due to a combination of the small sample size and weak effects. Hence, either no difference or a very small difference exists between the two groups. Third, it is also possible that the reporters may not have considered including calcium products in their MedWatch reports. Fourth, AERS data do not provide sufficient information to calculate incidence rates due to the nature of passive, voluntary reporting to MedWatch and the lack of a denominator (utilization). Fifth, the methods used to categorize the likelihood of events attributed to the drug, while they are systematic, remain subjective. Specifically, our modified definition of “probable” cannot be interpreted literally, as it is only closer to causal in a spectrum ranging from unrelated-associated to causal. Finally, it is possible that clinicians might

have recognized embolic phenomena with CRO and calcium but were unwilling to report them secondary to eventual favorable clinical outcomes or time constraints. It has been estimated that due to the voluntary, passive surveillance design of the MedWatch system, <10% of adverse events are reported to the FDA (21). The inability to distinguish rare from underreported events underscores the need for improved post-marketing surveillance.

Conclusions. In conclusion, our evaluation revealed a relative lack of evidence to support a serum precipitation event between CRO and calcium in adults. A causal relationship seems to exist for infants receiving CRO, but these findings have not been identified in the adult population. Our results reinforce the new FDA recommendations. Despite this, our analysis does not exclude the possibility that such an ADE could exist in adults; a biological gradient appears to be present, with scenarios that result in supranormal CRO and calcium concentrations placing recipients at the highest theoretical risk. Therefore, we recommend that individuals subject to intravascular depletion not be given sequential infusions of CRO and calcium. Continued active surveillance of this potential ADE, as suggested by the FDA, is prudent.

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None of us has conflicts of interest to declare.

REFERENCES

1. Agence Française de Sécurité Sanitaire des Produits de Santé. 2006. Commission Nationale De Pharmacovigilance. Compte rendu de la réunion du mardi 31 Janvier 2006. http://www.afssaps.fr/var/afssaps_site/storage/original/application/9a61d1bc834c126780061cd16e2ba91.pdf. Accessed 23 May 2009.
2. Anonymous. 2008. Second meeting of the Subcommittee of the Expert Committee on the Selection and Use of Essential Medicines. http://www.who.int/selection_medicines/committees/subcommittee/2/Ceftriaxone.pdf. Accessed 23 August 2008.
3. Anonymous. 1970. Blood volume, p. 555. In K. Diem and C. Lentner (ed.), Scientific tables, 7th ed. J. R. Geigy S.A., Basel, Switzerland.
4. Avci, Z., A. Koktener, N. Uras, F. Catal, A. Karadag, O. Tekin, H. Degirmencioglu, and E. Baskin. 2004. Nephrolithiasis associated with ceftriaxone therapy: a prospective study in 51 children. *Arch. Dis. Child.* 89:1069-1072.
5. Bennett, C. L., J. R. Nebeker, P. R. Yarnold, C. C. Tigue, D. A. Dorr, J. M. McKoy, B. J. Edwards, J. F. Hurdle, D. P. West, D. T. Lau, C. Angelotta, S. A. Weitzman, S. M. Belknap, B. Djulbegovic, M. S. Tallman, T. M. Kuzel, A. B. Benson, A. Evens, S. M. Trifilio, D. M. Courtney, and D. W. Raisch. 2007. Evaluation of serious adverse drug reactions: a proactive pharmacovigilance program (RADAR) vs safety activities conducted by the Food and Drug Administration and pharmaceutical manufacturers. *Arch. Intern. Med.* 167:1041-1049.
6. Bickford, C. L., and A. P. Spencer. 2005. Biliary sludge and hyperbilirubinemia associated with ceftriaxone in an adult: case report and review of the literature. *Pharmacotherapy* 25:1389-1395.
7. Bonapace, C. R., S. Fowler, K. A. Laessig, J. A. Lazor, and S. Nambiar. 2009. Ceftriaxone and calcium-containing fluids-rationale for product label changes, abstr. A1-008. Abstr. 49th Intersci. Conf. Antimicrob. Agents Chemother. American Society for Microbiology, Washington, DC.

8. Bradley, J. S., R. T. Wassel, L. Lee, and S. Nambiar. 2009. Intravenous ceftriaxone and calcium in the neonate: assessing the risk for cardiopulmonary adverse events. *Pediatrics* **123**:e609–e613.
9. European Medicines Agency. 2009. Pharmacovigilance working party monthly report. September. <http://www.emea.europa.eu/pdfs/human/phvwp/59945009en.pdf>. Accessed 29 December 2009.
10. Gin, A. S., H. Wheaton, and B. Dalton. 2008. Clinical pharmaceuticals and calcium-ceftriaxone. *Ann. Pharmacother.* **42**:450–451.
11. Grasberger, H., B. Otto, and K. Loeschke. 2000. Ceftriaxone-associated nephrolithiasis. *Ann. Pharmacother.* **34**:1076–1077.
12. Infectious Diseases Society of America. 2004. Practice guidelines for the management of bacterial meningitis. <http://www.journals.uchicago.edu/doi/pdf/10.1086/425368>. Accessed 23 August 2008.
13. Infectious Diseases Society of America/American Thoracic Society. 2007. Consensus guidelines on the management of community-acquired pneumonia in adults. <http://www.journals.uchicago.edu/doi/pdf/10.1086/511159>. Accessed 23 August 2008.
14. Kim, Y. S., M. F. Kestell, and S. P. Lee. 1992. Gall-bladder sludge: lessons from ceftriaxone. *J. Gastroenterol. Hepatol.* **7**:618–621.
15. Lamb, H. M., D. Ormrod, L. J. Scott, and D. P. Figgitt. 2002. Ceftriaxone: an update of its use in the management of community-acquired and nosocomial infections. *Drugs* **62**:1041–1089.
16. Lexi-Comp. 2009. Calcium gluconate monograph. <http://online.lexi.com/crlsql/servlet/crlonline>. Accessed 16 March 2009.
17. McCracken, G. H., Jr., J. D. Siegel, N. Threlkeld, and M. Thomas. 1983. Ceftriaxone pharmacokinetics in newborn infants. *Antimicrob. Agents Chemother.* **23**:341–343.
18. Monte, S. V., W. A. Prescott, K. K. Johnson, L. Kuhman, and J. A. Paladino. 2008. Safety of ceftriaxone sodium at extremes of age. *Expert Opin. Drug Saf.* **7**:515–523.
19. National Cancer Institute. 2009. Cancer therapy program evaluation: common terminology criteria for adverse events v3.0. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Accessed 17 March 2009.
20. National Center for Health Statistics. 2000. CDC growth charts: United States. <http://cdc.gov/growthcharts>. Accessed 14 August 2008.
21. Nebeker, J. R., P. Barach, and M. H. Samore. 2004. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Ann. Intern. Med.* **140**:795–801.
22. Puzovic, M., and G. Hardy. 2008. Comment: clinical pharmaceuticals and calcium ceftriaxone. *Ann. Pharmacother.* **42**:1914.
23. Rapp, R. P., and R. Kuhn. 2007. Clinical pharmaceuticals and calcium ceftriaxone. *Ann. Pharmacother.* **41**:2072.
24. Roche Pharmaceuticals. 2009. Rocephin. Package insert. <http://www.rocheusa.com/products/rocephin/pi.pdf>. Accessed 16 April 2009.
25. Schaad, U. B., W. L. Hayton, and K. Stoeckel. 1985. Single-dose ceftriaxone kinetics in the newborn. *Clin. Pharmacol. Ther.* **37**:522–528.
26. Schaad, U. B., and K. Stoeckel. 1982. Single-dose pharmacokinetics of ceftriaxone in infants and young children. *Antimicrob. Agents Chemother.* **21**:248–253.
27. Shiffman, M. L., F. B. Keith, and E. W. Moore. 1990. Pathogenesis of ceftriaxone-associated biliary sludge. In vitro studies of calcium-ceftriaxone binding and solubility. *Gastroenterology* **99**:1772–1778.
28. U.S. Food and Drug Administration. 2009. Information for healthcare professionals: ceftriaxone (marketed at Rocephin and generics). <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm084263.htm>. Accessed 16 April 2009.
29. Wolters Kluwer Health. 2008. Ceftriaxone monograph. Facts and comparisons 4.0. Wolters Kluwer Health, St. Louis, MO. <http://online.factsandcomparisons.com/MonoDisp.aspx?monoID=fandc-hcp10432&inProdGen=true&quick=Ceftriaxone>. Accessed 23 August 2008.
30. Xia, Y., K. J. Lambert, C. D. Schteingart, J. J. Gu, and A. F. Hofmann. 1990. Concentrative biliary secretion of ceftriaxone. Inhibition of lipid secretion and precipitation of calcium ceftriaxone in bile. *Gastroenterology* **99**:454–465.
31. Yarnold, P. R. 1996. Discriminating geriatric and non-geriatric patients using functional status information: an example of classification tree analysis via UniODA. *Educ. Psychol. Meas.* **56**:656–667.
32. Yarnold, P. R., and R. C. Soltysik. 2005. Optimal data analysis. APA Books, Washington, DC.