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Use and safety of erythromycin and metoclopramide in hospitalized infants

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Abstract

Objective—Prokinetic medications are used in premature infants to promote motility and decrease time to full enteral feeding. Erythromycin and metoclopramide are the most commonly used prokinetic medications in the neonatal intensive care unit (NICU), but their safety profile is not well defined.

Methods—We conducted a large retrospective cohort study using data from 348 NICUs managed by the Pediatrix Medical Group. All infants exposed to ≥1 dose of erythromycin, metoclopramide, or both, from a cohort of 887,910 infants discharged between 1997 and 2012 were included. We collected laboratory and clinical information while infants were exposed to erythromycin or metoclopramide and described the frequency of laboratory abnormalities and clinical adverse events.

Results—Metoclopramide use increased from 1997–2005 and decreased from 2005–2012, while erythromycin use remained stable. Erythromycin use was most often associated with a diagnosis of feeding problem (40%), while metoclopramide was most often associated with a diagnosis of gastroesophageal reflux (59%). The most common laboratory adverse event during exposure to erythromycin or metoclopramide was hyperkalemia (8.6/1000 infant days on erythromycin and 11.0/1000 infant days on metoclopramide). Incidence of pyloric stenosis was greater with

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erythromycin than with metoclopramide (10/1095, 0.9% vs. 76/19,001, 0.4%, p=0.01), but odds were not significantly increased after adjusting for covariates (odds ratio=0.52 [95% CI: 0.26, 1.02], p=0.06). More infants experienced an adverse event while treated with metoclopramide than with erythromycin (odds ratio=1.21 [95% CI: 1.03, 1.43]).

Conclusion—Metoclopramide was associated with increased risk of adverse events compared to erythromycin. Studies are needed to confirm safety and effectiveness of both drugs in infants.

Feedings in the neonatal intensive care unit (NICU) can be challenging due to impaired gastric motility, symptomatic gastroesophageal reflux (GER), and difficulties with enteral feeding. Prokinetic agents are used to improve feeding tolerance in infants, despite a lack of data for their safety and efficacy. Erythromycin is a macrolide antibiotic that also acts as a motilin receptor agonist, thereby stimulating intestinal peristalsis (1). It is sometimes used to promote gut motility in infants with delayed gastric emptying, poor small bowel motility, or GER, although it is not labeled for this use by the Food and Drug Administration (FDA) in any age group (2). Of concern, erythromycin has been associated with pyloric stenosis in young infants (3,4) and prolongation of the QT interval in some patients (5,6). An alternative prokinetic drug, metoclopramide, is a dopamine receptor antagonist used to promote gastric emptying (7), as well as to increase lower esophageal sphincter tone (8), which can reduce GER (9–11). However, metoclopramide is not FDA-approved for any use in term or preterm infants and has been associated with serious adverse events related to dopaminergic dysregulation in patients of all ages (12). In February of 2009, the FDA issued a warning against chronic use of metoclopramide-containing products to treat gastrointestinal disorders because chronic use of metoclopramide was linked to tardive dyskinesia that did not resolve when the medication was stopped (12,13).

In spite of the knowledge gaps surrounding these drugs, both erythromycin and metoclopramide have been used in the NICU (14). It is unknown if infant characteristics influence provider choice in the selection of a prokinetic agent, nor has the safety profile of either drug been evaluated in a large population of infants.

We conducted a large retrospective multicenter cohort study to describe the patterns of use and the safety profiles of erythromycin and metoclopramide in hospitalized infants. We hypothesized that metoclopramide would be associated with higher odds of adverse events compared with erythromycin.

METHODS

Infants were included if they were discharged from 1 of the 348 NICUs managed by the Pediatrix Medical Group between 1997 and 2012 and received erythromycin, metoclopramide, or both during the first 120 days of life. Data were obtained from a database that is prospectively created from electronic medical records generated by clinicians on all infants cared for by the Pediatrix Medical Group (15). This database contains de-identified admission notes, daily progress notes, and discharge summaries, as well as maternal history, demographic data, medications, laboratory results, diagnoses, and procedures. Only infants with a diagnosis of GER, dysmotility, delayed gastric emptying, feeding problem, or aspiration were included, and only days of exposure to the drugs of

interest after the inclusion diagnosis was made were evaluated. We excluded infants who received erythromycin during the first 2 days of life in an attempt to remove infants more likely to receive erythromycin as an antimicrobial than a prokinetic; infants with major congenital anomalies were also excluded. Infants were categorized based on having ever received erythromycin or metoclopramide.

We determined the median gestational age, birth weight, postnatal age at first drug exposure, and duration of therapy. Age at first exposure was defined as the postnatal age in days at the time of first exposure to either of the drugs of interest. Duration of treatment was defined as the total number of days each infant was exposed to the medication of interest. We determined the distribution of each gastrointestinal indication and the most common concomitant medications for both drugs. Infants who were prescribed the drug of interest on the day of discharge were considered as having been discharged home on the drug. Changes in use over time were determined by comparing the annual proportion of patients treated with each medication of interest.

The safety of each drug was evaluated by determining the incidence of adverse events (AEs) and serious adverse events (SAEs) for both laboratory and clinical parameters. A laboratory AE was any laboratory abnormality occurring while the infant was exposed to the medication of interest (Appendix, http://links.lww.com/MPG/A451). We counted each day with a laboratory abnormality as a separate laboratory AE or SAE. Both the proportion of infants experiencing a laboratory AE or SAE and the proportion of days with an event were calculated. A clinical AE was any diagnosis of rash, seizure, arrhythmia, focal intestinal perforation, surgical or medical necrotizing enterocolitis (NEC), pyloric stenosis, or grade III or IV intraventricular hemorrhage that occurred while an infant was exposed to the medication of interest. We counted each new episode of a diagnosis as a separate AE. Consecutive days with the same clinical diagnosis of interest were considered to be a single clinical AE. No distinction was made between AE and SAE for clinical events. Death was defined as death before NICU discharge.

We used standard summary statistics including counts, percentages, medians, and interquartile ranges to describe the study variables. The distribution of categorical and continuous variables was compared between groups using chi-square, Fisher’s exact, Wilcoxon rank sum, and Kruskal-Wallis tests where appropriate. We used multivariable logistic regression to evaluate the association between the drug of interest and the presence of any AE or SAE, controlling for gestational age at birth, postnatal age at the time of first drug exposure, small-for-gestational-age status, and exposure to inotropes or mechanical ventilation on the first day of drug exposure. Stata 12.0 (College Station, TX) was used to perform all statistical analyses, and a $p<0.05$ was considered statistically significant. This study was approved by the Duke University Institutional Review Board.

RESULTS

We identified 20,196 infants treated with erythromycin or metoclopramide (Table 1). The number of infants who ever received metoclopramide was 10-fold higher than the number who ever received erythromycin: 19,200/20,196 (95%) vs. 1587/20,196 (8%). Five hundred

and ninety one infants were exposed to both drugs. These infants contributed 19,528 days of erythromycin exposure, 261,094 days of metoclopramide exposure, and 3271 days of concomitant exposure. Infants treated with erythromycin had a lower median birth weight and gestational age compared to those treated with metoclopramide: 1320 g (interquartile range; 970, 1740) vs. 1476 g (1016, 2152), p<0.001, and 29 weeks (27, 32) vs. 31 (28, 34), p<0.001. Most infants exposed to either drug were between 7 and 29 days of age when first exposed: 811/1587 (51%) for erythromycin and 10,243/19,200 (53%) for metoclopramide. A total of 1095 infants were first exposed to erythromycin and 19,001 were first exposed to metoclopramide. The median duration of exposure was 6 days (1, 10) for erythromycin and 8 (1, 20) for metoclopramide. Ten percent of infants exposed to metoclopramide were treated for >30 days. Erythromycin use was most commonly associated with a diagnosis of feeding problem (40%), while metoclopramide was most commonly associated with GER (59%).

Use by Year

The proportion of infants treated with metoclopramide increased to a peak of 2192/55,613 (4%) in 2005 and decreased to a low of 169/85,938 (0.2%) in 2012 (Figure 1). Erythromycin use has steadily increased from 8/10,557 (0.1%) in 1997 to approximately 200 infants per year since 2010 (0.4%). It was used in more infants than metoclopramide in 2012: 225/85,938 (0.3%) vs. 169/85,938 (0.2%).

Concomitant Medications

Caffeine citrate was the most common concomitant medication for both metoclopramide and erythromycin (Table 2). Ranitidine was frequently used along with metoclopramide (31% of metoclopramide days) but less frequently used with erythromycin (9% of erythromycin days). Respiratory medications, such as betamethasone, albuterol, and aminophylline, and antimicrobials, especially vancomycin, were frequently used with both erythromycin and metoclopramide.

Adverse Events

Laboratory AEs were uncommon for both erythromycin and metoclopramide: 33.8/1000 infant days and 34.2/1000 infant days respectively, p=0.34 (Table 3). The most common laboratory AEs while exposed to either erythromycin or metoclopramide were hyperkalemia (8.6 and 11.0/1000 infant days, respectively, p=0.002), hypocalcemia (5.4 and 4.4/1000 infant days, respectively, p=0.03), direct hyperbilirubinemia (4.9 and 4.6/1000 infant days, respectively, p=0.54), and elevated gamma-glutamyl transpeptidase (3.0 and 3.0/1000 infant days, respectively, p=0.99). White blood cell count abnormalities were similar with both drugs (6.8/1000 infant days vs. 6.8/1000 infant days). The proportion of infants experiencing at least 1 laboratory AE was lower for erythromycin compared to metoclopramide (178/1095 [16%] vs. 3881/19,001 [20%], p<0.01). SAEs were uncommon for both drugs. Hypocalcemia was the most common laboratory SAE while exposed to either erythromycin or metoclopramide (3.0/1000 infant days and 2.4/1000 infant days, p=0.10). The proportion of infants experiencing at least 1 laboratory SAE was lower for erythromycin than metoclopramide (45/1095 [4%] vs. 1078/19,001 [6%], respectively, p=0.03).

Medical NEC was the most common clinical AE (8/1095 [0.7%] for erythromycin and 279/19,001 [1.5%] for metoclopramide, p=0.05) (Table 4). The proportion of infants developing pyloric stenosis was low, and but it did occur more frequently with erythromycin exposure than with metoclopramide (10/1095 [0.9%] and 76/19,001 [0.4%], p=0.01). None of the infants who received erythromycin in the first week of life developed pyloric stenosis (0/123). Arrhythmia was rarely reported with either drug (1/1095 [0.1%] for erythromycin and 25/19,001 [0.1%] for metoclopramide, p=0.72).

On multivariable analysis, infants treated with metoclopramide had a greater odds of experiencing the composite outcome of any laboratory AE, SAE, or clinical AE compared to those treated with erythromycin (odds ratio [OR]=1.21 [95% confidence interval; 1.03, 1.43], p=0.02). This was primarily driven by a greater odds of a laboratory AE (OR=1.21 [1.03, 1.44], p=0.02) in infants treated with metoclopramide. The odds of a laboratory SAE or a clinical AE were also greater for infants receiving metoclopramide, but this failed to reach statistical significance (OR=1.25 [0.92, 1.71], p=0.15 and OR=1.45 [0.93, 2.26], p=0.1). The odds of pyloric stenosis was lower for infants exposed to metoclopramide but did not reach statistical significance (OR=0.52 [0.26, 1.02], p=0.06).

Discharge Home

Infants treated in the NICU with erythromycin were less likely to be discharged home on the medication compared to those treated with metoclopramide (140/1095 [13%] vs. 3198/19,001 [17%], p<0.001). The most common diagnosis in infants discharged home on metoclopramide was GER (2003/3198, 63%). Feeding problems were the most common diagnosis in infants discharged home on erythromycin (57/140, 41%).

DISCUSSION

This large cohort study describes the use and safety of prokinetic agents in hospitalized infants. While metoclopramide was used more frequently in the earlier phase of the study, its use has decreased sharply and erythromycin was the more commonly used agent in the later part of the study. Infants exposed to erythromycin had a lower gestational age and birth weight and suffered fewer laboratory and overall AEs compared those exposed to metoclopramide. Pyloric stenosis occurred more frequently with erythromycin exposure than with metoclopramide, but this finding was not significant when adjusted for gestational age at birth, small-for-gestational-age status, surrogates of severity of illness, and age at first medication exposure. Infants were more likely to be discharged home on metoclopramide than erythromycin. The differences in the safety profile of both drugs should be considered by clinicians when prescribing prokinetic medications.

The safety and efficacy of erythromycin in infants is incompletely characterized. Erythromycin may improve feeding tolerance, leading to faster achievement of full enteral feeds (16–19). This effect is thought to be through stimulation of the motilin receptors in the intestinal wall, which induce peristalsis (1). Despite this theoretical benefit, clinical trials evaluating the efficacy of erythromycin have demonstrated conflicting results. Sample size limitations, significant variability in timing of erythromycin initiation, either prophylactically or in response to clinical symptoms, as well as a wide range of

recommended doses may explain the inconsistent results (16–23). A double-blinded, randomized, controlled trial found benefit for 12 infants >32 weeks gestation and no difference from placebo for 13 infants <32 weeks (16). Another open-label, randomized, controlled trial found the opposite effect, with benefit for 9 infants <32 weeks and no improvement for 21 infants >32 weeks gestational age (22). In our cohort, 65% of infants treated with erythromycin were <32 weeks gestation, and 71% were <1 month of age.

Safety data on erythromycin use in infants are limited and have focused on select adverse events. Pyloric stenosis is one of the adverse event of special interest in infants exposed to erythromycin. The same motilin receptor stimulation responsible for the therapeutic effects of erythromycin is thought to lead to excessive gastric muscle contraction with subsequent hypertrophy and pyloric obstruction (1). A large retrospective cohort study observed a relative risk of pyloric stenosis of 10.5 for infants exposed to erythromycin during the first 2 weeks of life (3). In our cohort, despite frequent exposure to erythromycin in the first month of life, pyloric stenosis was uncommon (0.9%). In fact, this incidence was similar to the one reported for infants without erythromycin exposure and we did not find increased odds of pyloric stenosis in infants exposed to erythromycin compared to those exposed to metoclopramide (3). Our findings are similar to two prospective studies treating 29 and 91 premature infants with high-dose erythromycin (50 mg/kg/day), where none of the infants developed pyloric stenosis (19,24). It has been suggested that the association between early erythromycin exposure and the incidence of pyloric stenosis may be less pronounced in premature than in term infants (4). The high proportion (>75%) of infants ≤32 weeks GA in our erythromycin exposed cohort may further explain why we did not observe an association with pyloric stenosis. Other adverse events of special interest in infants exposed to erythromycin include NEC and cardiac dysrhythmias. Previous randomized trials have demonstrated no significant differences in the incidence of NEC between infants treated with erythromycin and those given placebo (20,21,23). Other studies found no increase in the incidence of cardiac arrhythmia, but sample sizes were small and evaluation for AEs was not performed in a systematic way, possibly resulting in a reduced event detection rate (20,23,25). In our large cohort, the incidence of both conditions was low, and none occurred more frequently with erythromycin exposure compared to metoclopramide exposure.

Data on the safety and efficacy of metoclopramide in infants is similarly lacking. Metoclopramide increases gastroesophageal sphincter tone through inhibition of dopamine receptors, which increases tissue sensitivity to acetylcholine leading to improved peristalsis and decreased risk of GER (12). Randomized trials in infants have used doses ranging from 0.1 mg/kg/day to 0.9 mg/kg/day with variable reported efficacy (10,26). A placebo-controlled trial of 30 infants found a reduction in reflux index scores with a dose of 0.4 mg/kg/day (11). Another study of 28 infants with a mean age of 9 months found that treated infants had more frequent reflux events at a dose of 0.5 mg/kg/day (8).

The safety of metoclopramide in infants has not been well described, as previous trials were likely underpowered to detect adverse events. Reported events from these trials in infants included rare occurrences of irritability, oculogyric crisis, and dystonic reaction (7–9,26–31). Dystonic reactions, tardive dyskinesia, and neuroleptic malignant syndrome are potentially serious adverse events that have also been reported in case reports of infants with

metoclopramide exposure (27–29). In 2009, the FDA issued a black box warning for metoclopramide due to potential for tardive dyskinesia and other adverse neurologic effects (13). In our cohort, patients treated with metoclopramide did have increased odds of any AE or SAE compared to those treated with erythromycin. Dystonic reactions, oculogyric crisis, and tardive dyskinesia were not reported in the 19,200 infants treated with metoclopramide in our study. While the overall incidence of adverse events while on metoclopramide is low, the severity of possible neurologic side effects has led many groups to recommend against its use (32–35).

We initially observed a sharp increase in metoclopramide use from 1997–2004 followed by a steady decline. In 2000, cisapride, an effective prokinetic agent, was removed from the market due to cardiac side effects (36,37). Metoclopramide use increased significantly shortly after this, likely reflecting the therapeutic hole left by the withdrawal of cisapride (38). Beginning in 2005, the proportion of infants treated with metoclopramide has steadily declined. The decrease in use was temporally associated with clinical quality improvement efforts to limit the use of metoclopramide in Pediatrix NICUs (39). The sharpest drop off occurred after the FDA issued black box warning on metoclopramide (13,27,35,40).

The strengths of our study include the use of a large, diverse, multicenter cohort of infants. This sample size allowed us to assess the incidence of uncommon AEs, for which prior clinical trials may have been underpowered. The analysis of events on a daily level allowed us to determine the frequency with which AEs occurred, in addition to the proportion of infants affected. We were able to use multivariable modeling to control for severity of illness by including markers such as small-for-gestational-age status and gestational age, and surrogates of severity of illness such as inotropic support and mechanical ventilation. However, differences in the frequency of AEs could be related to unmeasured comorbidities, use of additional therapies, or other medications that were not considered in the analysis. Laboratory AEs may be affected by the frequency of laboratory draws, which is determined by clinician preference. Information about drug dosing amount and interval was not available, which limited our ability to evaluate dose-related differences in AEs. We also limited our evaluation of AEs only to days of drug exposure and did not evaluate the prevalence of delayed AEs occurring after the medication is stopped. Unreported AEs, including dystonic reaction, irritability, and fussiness, may have been missed. Lastly, our study does not provide any information about the efficacy of erythromycin or metoclopramide. Lack of information about meaningful efficacy end points—such as clinical signs of GER and details about feeding tolerance including volume of feeds, routes, and caloric density—precluded this type of analysis using this database.

CONCLUSION

Metoclopramide was associated with increased risk of laboratory AEs and SAEs compared to erythromycin, while the risk of clinical AEs was similar between the 2 drugs. Metoclopramide use has decreased sharply over the last few years. Additional studies are needed to confirm the safety, effectiveness, and proper dosing of both of these drugs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Dr. Ericson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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What We Know

- Prokinetic medications are sometimes used in infants with feeding problems and gastroesophageal reflux.
- Metoclopramide and erythromycin are the most commonly used prokinetic medications in infants, but safety is not well established for either drug.
- Metoclopramide has a black-box warning due to potential for neurologic side effects.

New Findings

- Metoclopramide use has decreased since 2005.
- Metoclopramide is associated with higher odds of adverse events than erythromycin.
- The odds of developing pyloric stenosis are similar in infants exposed to either drug.

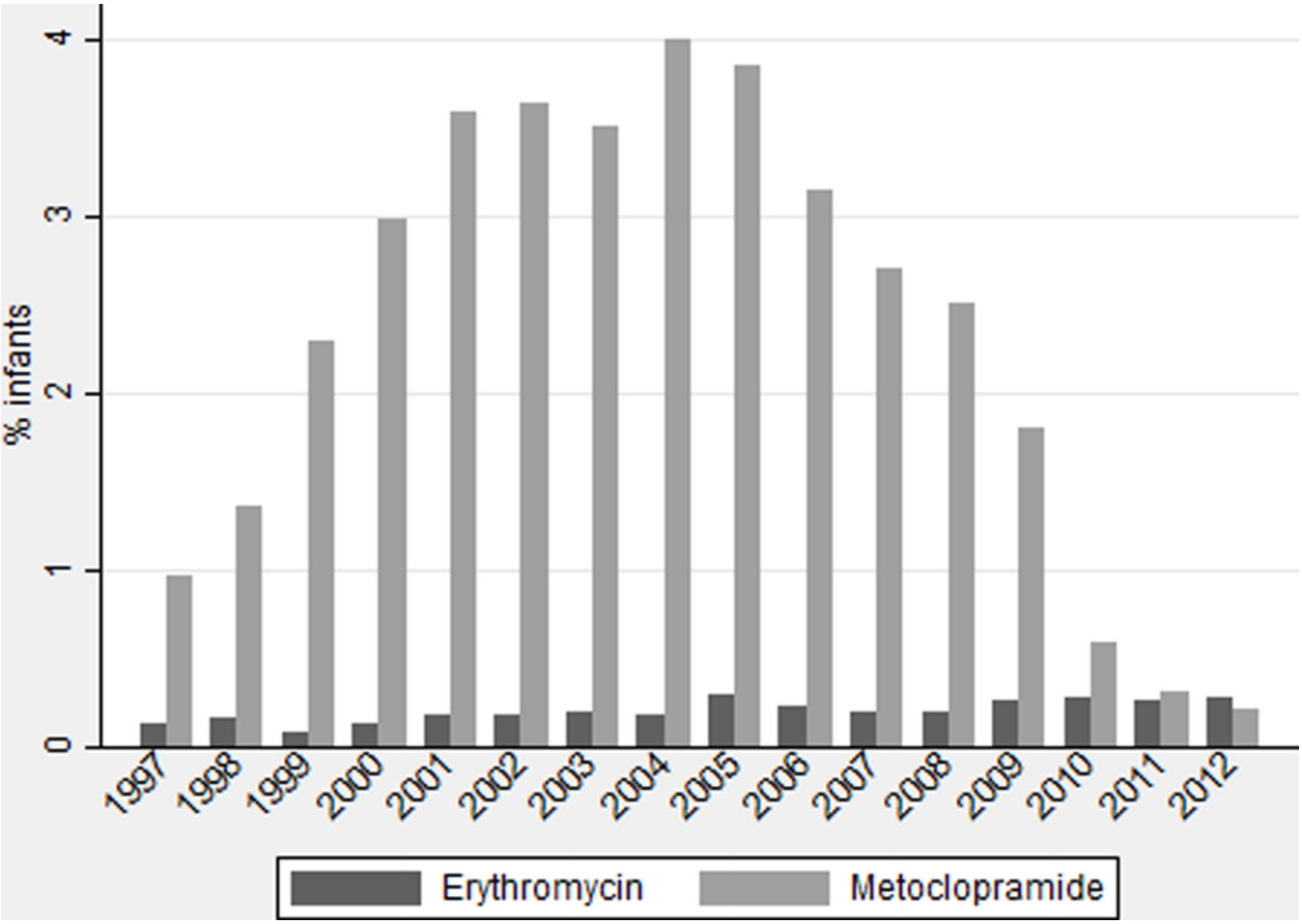

Figure 1.
Infants treated with erythromycin and metoclopramide by year of discharge.

TABLE 1

Demographics for infants exposed to erythromycin and metoclopramide

	Erythromycin N=1587 (%)	Metoclopramide N=19,200 (%)
Gestational age, weeks		
<26	188 (12)	1708 (9)
26–28	450 (28)	4317 (22)
29–32	610 (38)	6394 (33)
33–36	218 (14)	4030 (21)
≥37	119 (8)	2737 (14)
Birth weight, g		
<1000	498 (31)	4592 (24)
1000–1499	540 (34)	5234 (27)
1500–2499	388 (24)	5819 (30)
2500–3499	107 (7)	2533 (13)
≥3500	54 (3)	984 (5)
Age at first exposure, days		
3–6	123 (8)	3033 (16)
7–29	811 (51)	10,243 (53)
30–59	404 (25)	3771 (20)
60–120	248 (16)	1823 (9)
Duration of exposure, days*	6 (1, 10)	8 (1, 20)
Race/ethnicity		
White	541 (51)	9359 (50)
African American	273 (26)	3261 (17)
Hispanic	200 (19)	4992 (27)
Other	45 (4)	964 (5)
Male	873 (55)	10,643 (55)
Inborn	1294 (82)	15,198 (81)
Caesarean section	1073 (68)	12,172 (64)
Small for gestational age	236 (15)	2458 (13)
Died	11 (1)	168 (1)
Discharged on medication	140 (13)	3198 (17)

*Median (interquartile range).

TABLE 2

Most Frequent Concomitant Medications (% Days Receiving Medication)

Erythromycin N=20,523 days	**Metoclopramide N=261,094 days**
Caffeine citrate (36)	Caffeine citrate (37)
Vitamin A (27)	Ranitidine (31)
Levothyroxine (21)	Epoietin alpha (17)
Furosemide (18)	Aminophylline (10)
Epoietin alpha (11)	Vancomycin (8)
Fluconazole (9)	Spironolactone (7)
Ranitidine (9)	Furosemide (7)
Vancomycin (8)	Gentamicin (6)
Phenobarbital (5)	Chlorothiazide (5)
Gentamicin (4)	Phenobarbital (4)

TABLE 3

Incidence of Laboratory Adverse Events for Days on Erythromycin or Metoclopramide

	Incidence (/1000 infant days)					
	AE			SAE		
	Erythromycin	Metoclopramide	P	Erythromycin	Metoclopramide	P
Serum electrolytes						
Hyperglycemia	0.5	0.3	0.08	0.1	0.0	0.92
Hypoglycemia	1.3	1.3	0.95	0.5	0.2	<0.01
Hypernatremia	0.5	0.6	0.47	0.0	0.1	0.22
Hyponatremia	0.5	0.7	0.36	0.1	0.0	0.85
Hyperkalemia	8.6	11.0	<0.01	0.5	0.9	0.08
Hypokalemia	2.3	2.0	0.37	0.2	0.4	0.27
Hypercalcemia	0.1	0.1	0.97	0.0	0.0	0.47
Hypocalcemia	5.4	4.4	0.03	3.0	2.4	0.10
Hypermagnesemia	0.1	0.2	0.27	0.1	0.1	0.69
Hypomagnesemia	0.3	0.3	0.91	0.1	0.1	0.91
Hyperphosphatemia	0.3	0.2	0.25	0.1	0.1	0.73
Hypophosphatemia	2.0	1.8	0.52	0.4	0.3	0.62
Renal function						
Elevated BUN	0.6	0.2	<0.01	0.1	0.1	0.49
Elevated creatinine	0.7	0.7	0.70	0.3	0.3	0.74
Liver function						
Elevated AST	0.0	0.0	0.64	0.0	0.0	
Elevated ALT	0.5	0.1	<0.01	0.1	0.0	0.03
Elevated GGT	3.0	3.0	1.00	1.3	1.2	0.66
Elevated direct bilirubin	4.9	4.6	0.54	0.8	1.2	0.15
Blood counts						
Leukocytosis	5.4	4.4	0.04	1.1	0.5	<0.01
Leukopenia	1.3	2.0	0.04	0.1	0.1	0.28
Neutropenia	0.1	0.4	0.02	0.0	0.1	0.23

	Incidence (/1000 infant days)					
	AE			SAE		
	Erythromycin	Metoclopramide	P	Erythromycin	Metoclopramide	P
Any laboratory abnormality	33.8	34.2	0.78	8.3	7.7	0.34

Abbreviations: AE, adverse event; SAE, severe adverse event; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma glutamyltransferase.

TABLE 4

Infants with a Clinical Adverse Event While on Erythromycin or Metoclopramide

	Erythromycin %	Metoclopramide %	P
Rash	0.6	0.5	0.71
Focal intestinal perforation	0.0	0.3	0.56
Surgical necrotizing enterocolitis	0.0	0.3	0.07
Medical necrotizing enterocolitis	0.7	1.5	0.05
Seizure	0.2	0.6	0.07
Grade III–IV intraventricular hemorrhage	0.4	0.2	0.19
Arrhythmia	0.1	0.1	0.72
Pyloric stenosis	0.9	0.4	0.01
Any clinical adverse event	1.9	3.1	0.03