Articles

Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin: a case review and cohort study

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Summary

Background In February, 1999, a local US health department identified a cluster of pertussis cases among neonates born at a community hospital and recommended oral erythromycin for post-exposure prophylaxis for about 200 neonates born at that hospital between Feb 1 and Feb 24, 1999. We investigated a cluster of seven cases of infantile hypertrophic pyloric stenosis (IHPS) that occurred the following month among the neonates who had received erythromycin.

Methods We obtained a masked, independent review of the IHPS ultrasonography diagnoses, calculated the monthly IHPS incidence, and compared index and historical (1998–99) IHPS cases with respect to several characteristics including erythromycin exposure. We used a retrospective cohort of infants born in January and February, 1999, to investigate further erythromycin exposure and development of IHPS.

Findings An independent review confirmed the ultrasonographic diagnoses of all seven index IHPS cases. All index cases versus none of the historical IHPS cases had been given erythromycin for pertussis prophylaxis. The IHPS rate for infants born in the hospital in February, 1999, was 32·3 per 1000 liveborn infants, representing nearly a seven-fold increase over 1997–98 (relative risk 6·8 [95% CI 3·0–15·7]). Among infants born in January and February, 1999, erythromycin was associated with IHPS (absolute risk 4·5%, relative risk ∞ [1·7–∞]).

Interpretation Neonates receiving oral erythromycin may have an increased risk of IHPS. The risks and benefits of erythromycin for neonatal pertussis prophylaxis should be re-evaluated, and caution should be used in defining risk groups for prophylaxis.

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Introduction

Infantile hypertrophic pyloric stenosis (IHPS) is hypertrophy of the pyloric muscle that usually results in non-bilious, projectile vomiting. Symptoms of IHPS begin in most cases at about 3·5 weeks of age,[1] although in rare cases symptoms may occur shortly after birth.[2] Premature infants develop IHPS symptoms later than term infants.[3–5] IHPS affects about one to three infants per 1000 liveborn infants and affects about four to five times as many boys as girls.[3–6] Surgical treatment for IHPS is safe and effective.[7] Although some reports have suggested a possible link between erythromycin and IHPS,[8,9] the cause of the disorder remains unknown.

In February, 1999, physicians diagnosed pertussis in six infants who were about 2 weeks of age and had been born that month in a community hospital in the USA. The source of the infection was presumed to be a staff member working in the nursery at the hospital. On Feb 25, 1999, the local health department recommended erythromycin prophylaxis for all infants born at the hospital from Feb 1 to Feb 24, 1999, based on the current American Academy of Pediatrics recommendations.[10] The recommendation was extended to infants born in the last 2 weeks of January at the hospital and who had any pertussis symptoms. The community hospital has about 215 births per month, and is one of six maternity units in a metropolitan area of about 350 000 people.

In late March, paediatric surgeons at another hospital recognised that they had operated on seven infants with pyloric stenosis within a 2-week period, that all seven infants had been born in the community hospital, and all had been treated prophylactically with erythromycin. The hospital in which the surgery was done is one of two hospitals in the metropolitan area that have paediatric surgery services.

The state health department requested assistance from the Centers for Disease Control and Prevention. The county health department and the Centers for Disease Control and Prevention launched this investigation to assess the possible association between erythromycin prophylaxis and subsequent surgery for pyloric stenosis.

Methods

Case review

To validate the diagnoses, we did a masked review of ultrasonography scans for the seven IHPS cases originally identified at surgery, as well as for seven negative ultrasonography scans of the pylorus from the same hospital during the same period. The 14 ultrasonography scans were reviewed by a paediatric radiologist in another state who was unaware of the original readings. The reviewing radiologist marked each scan as either positive or negative for IHPS. The degree of agreement between the initial and masked readings was assessed with the κ statistic by standard methods.

Historical comparison

To compare the history and diagnostic features of the seven index IHPS cases with historical IHPS cases, we did a detailed chart review at the two hospitals in the region at which infantile pyloromyotomies are done. We used a hospital diagnosis of pyloric stenosis (International Classification of Diseases, ninth revision, code 750.5) that required pyloromyotomy in infants born in one of the six maternity units in the region during 1998 or 1999 to ascertain IHPS cases. Hospital administrative staff identified the cases through searches of computerised hospital records. We reviewed the paediatric hospital records and the mother's and infant's hospital birth records for the seven index cases originally identified from the Feb 1 to Feb 24, 1999, birth cohort of the community hospital. We reviewed only the paediatric hospital records for 40 IHPS cases diagnosed in 1998, and January to April, 1999, that were not part of the February birth cohort of the community hospital. Abstracted information on index and historical IHPS cases included history of use of erythromycin or other medications. We used Fisher's exact test to evaluate the differences between index and historical cases based on information derived from paediatric hospital records.

To calculate 1997 IHPS rates and assess further the background risk of IHPS in this region, we did a rapid chart review without detailed abstraction for all 1997 IHPS cases using the same case definition as above. We calculated the number of IHPS cases per 1000 liveborn infants for each month among infants born at the community hospital and infants born at any of the other five maternity units in the region for 1997–99, using the number of liveborn infants at the respective units as the denominator.

Cohort study

We also did a retrospective cohort study of infants born in January and February, 1999, at the community hospital to assess the relation between erythromycin use and gastrointestinal illnesses, including a diagnosis of IHPS. We restricted the February births to infants born between Feb 1 and Feb 24 since this period corresponded to the erythromycin recommendation. We attempted to contact only about 75% of the January births owing to time and resource limitations.

Although gastrointestinal side-effects of erythromycin are well documented, we asked about these symptoms for several reasons: to quantify the extent of gastrointestinal symptoms in neonates caused by oral erythromycin in this setting; to look for additional IHPS cases that may not have been identified by surgeons as part of the original cluster; and to identify symptoms that may represent part of the causal pathway of IHPS, even though these symptoms are not specific to IHPS.

From April 20 to April 26, 1999, public-health nurses from the local health department contacted mothers of infants born at the community hospital in January and February, 1999, and interviewed mothers by telephone. In a few cases, the mother was unavailable and the father was interviewed. The nurses asked about the infant's use of erythromycin, including dose and duration, and they also asked for the name of the pharmacy from which the drug was purchased so that prescription details could be completed if necessary. The interview also included questions on gastrointestinal symptoms (ie, vomiting, irritability with feeding) and any association that had been seen between these symptoms and erythromycin use. Vomiting was defined as a large amount of emesis that was different from the infant's usual pattern. The mothers of all seven index IHPS cases exposed to erythromycin were interviewed as part of the cohort study. Respondents were not told about a possible association between erythromycin and IHPS.

We calculated the crude relative risk for erythromycin exposures and possible adverse outcomes. 95% CI were calculated by the Mantel-Haenszel variance estimator with SAS version 6.12. We adjusted data for sex, gestation, and possible exposure to pertussis, but this adjustment did not alter the point estimates or 95% CIs meaningfully; therefore, crude relative risks are shown. We used StatXact version 3 for Windows to calculate the exact lower bound of the 95% CI for the relative risk of IHPS.

Characteristic	Index cases (n=7)	Historical cases (n=40)	p
Risk factors			
Male sex	6 (86%)	31 (78%)	0·53
Gestational age <38 weeks	0	12 (30%)	0·11
Family history of IHPS	0	7 (18%)	0·30
Received erythromycin	7 (100%)	0	<0·0001
Received other antibiotics	0	4 (10%)	0·51
Received simethicone, cisapride, or ranitidine before IHPS admission	1 (14%)	7 (18%)	0·66
Maternal history of illicit drug use	0	2 (5%)	0·72
Primary diet at IHPS admission			
Exclusively breastfed	2 (29%)	5 (13%)	0·28
Exclusively bottle-fed	4 (57%)	29 (73%)	0·34
Combination	1 (14%)	6 (15%)	0·72
Age at hospital admission for IHPS (days)			
Median (range)	24 (14–42)	34·5 (11–72)	
Mean (SD)	25·6 (8·8)	35·4 (14·5)	0·09*
Diagnostic features of IHPS			
Projectile vomiting	2 (29%)	30 (75%)	0·03
Vomiting with feeding	5 (71%)	31 (78%)	0·53
Bilious vomiting	0	1 (3%)	0·85
Blood in vomit	1 (14%)	5 (13%)	0·64
Hypochloraemia†	2 (29%)	6 (15%)	0·34
Metabolic alkalosis‡	4 (57%)	10 (25%)	0·11
Duration of vomiting (days)			
Median (range)	3·5 (2–5)	5 (1–29)	
Mean (SD)	3·7 (1·2)	6·9 (6·1)	0·20*
Mean pyloric thickness (mm)§	4·8	4·5	0·45*
Mean pyloric length (mm)§	19·7	18·9	0·38*

*Differences in means based on pooled variances. †Serum chloride <96 mmol/L. ‡Serum hydrogen carbonate >29 mmol/L. §Measured by ultrasonography.

Table 1: **Characteristics of index and historical cases of IHPS**

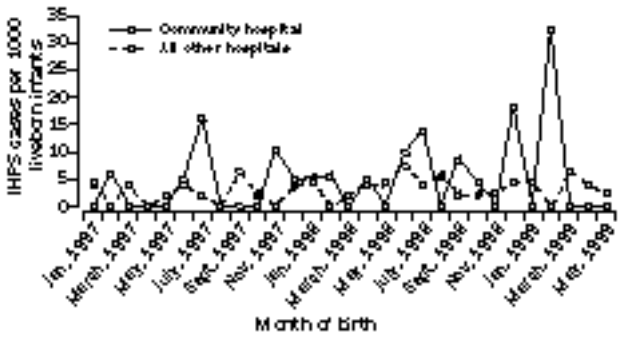
Results

Case review

The masked, independent review of the 14 ultrasonography scans showed 100% agreement between the radiologists of the hospital at which surgery was done and the reviewing radiologist (κ=1·0 [95% CI 0·48–1·0]). The initial chart review of the seven index IHPS cases indicated that all were full-term infants with birthweights ranging from 3·1 kg to 4·4 kg, all had routine newborn hospital stays, none of the mothers reported tobacco use during pregnancy, and only one mother reported any alcohol use during pregnancy. None of these infants had been diagnosed as having pertussis, but all seven had received erythromycin for pertussis prophylaxis. The infants were 2–17 days old when erythromycin was started, and began erythromycin a mean 16·3 days (range 10–25) before being admitted for IHPS. IHPS diagnoses and subsequent pyloromyotomy of the index cases were managed by three paediatric surgeons and three radiologists. All seven index cases had a preoperative diagnosis of IHPS, pyloric ultrasonography unequivocally interpreted as IHPS, and surgical confirmation of the diagnosis. Six of the seven cases presented with the non-bilious vomiting that is characteristic of IHPS. Although the seventh infant had negligible vomiting, consistent with typical infant regurgitation, his primary symptom was excessive irritability with feeding. A 7 mm endoscope could not pass through the pylorus, so ultrasonography was done and was positive for IHPS.

Historical comparison

Chart review at the two hospitals with paediatric surgical services identified 40 IHPS cases diagnosed in 1998–99 in addition to the seven index IHPS cases born in



Monthly incidence of IHPS among infants born in the community hospital versus infants born in other maternity units

February, 1999. All seven index IHPS cases versus none of the historical IHPS cases had received oral erythromycin (table 1). Although most of the differences were not significant, the index cases were less likely to have been born before 38 weeks' gestation, were less likely to have a family history of IHPS, and were younger on average at the time of IHPS diagnosis than the historical cases. The diagnostic features were similar, but index cases were less likely to have projectile vomiting than historical cases and more likely to have electrolyte imbalances (hypochloraemia and metabolic alkalosis), despite the fact that the index cases had fewer mean days of vomiting before admission to hospital than did historical IHPS cases. Mean pyloric thickness and length were similar for index and historical cases among infants with ultrasonographic measurements of the pylorus noted.

Among all infants born in one of the six maternity units, 22 born in 1997, 36 born in 1998, and 15 born between January and May, 1999, had IHPS. The rate of IHPS among infants born at the community hospital in February, 1999 (32·3 per 1000 liveborn infants) was nearly seven times higher than the rates for infants born at this hospital in 1997 and 1998 (4·7 per 1000 liveborn infants, relative risk 6·8 [95% CI 3·0–15·7]). Although there was substantial monthly variation in rates, there was a peak among February births at the community hospital (figure).

Cohort study

We attempted to contact the families of 349 infants (82%) born at the community hospital in January and February, 1999. We were able to complete interviews for 282 (81%), could not make contact by telephone for 64 (18%), and contacted three (1%) who chose not to participate. 157 infants had a history of oral erythromycin use, whereas 125 infants had never taken erythromycin. The prevalence of erythromycin use was 8·6% among infants born in January and 90·2% among infants born in February. We obtained complete information on preparation, dose, and duration of erythromycin use for 132 (84·1%) of 157 infants who took erythromycin, with this information provided either by the parent, who read information directly from the bottle, or by health-department staff, who contacted the pharmacy that dealt with the prescription. Erythromycin preparations given to the infants included ethylsuccinate (n=83), estolate (n=59), ethylsuccinate and estolate (n=1), and unknown (n=14).

Mothers were asked to report gastrointestinal symptoms that had occurred since birth that were different from their infant's usual pattern. Infants exposed to erythromycin were more likely to have irritability with feeding and vomiting, and to have been admitted to hospital for vomiting than infants who had not been exposed to erythromycin (table 2). There were seven pyloromyotomies for IHPS among erythromycin-exposed infants and none among infants not exposed to erythromycin. All seven index IHPS cases began having symptoms while taking erythromycin.

Outcome	Erythromycin exposure (n=157)	No erythromycin exposure (n=125)	Unadjusted relative risk (95% CI)
Irritability with feeding	34 (21·7%)	13 (10·4%)	2·1 (1·2–3·7)
Vomiting	49 (31·2%)	22 (17·6%)	1·8 (1·2–2·7)
Calling doctor about vomiting or irritability	47 (29·9%)	20 (16·0%)	1·9 (1·2–2·9)
Admitted to hospital for vomiting	10 (6·4%)	2 (1·6%)	4·0 (1·0–15·8)
Pyloromyotomy for IHPS	7 (4·5%)	0	∞ (1·7–∞)

Table 2: **Risk ratios for selected outcomes from birth to time of interview that were associated with erythromycin exposure among infants born at the community hospital**

The relative risk of being admitted to hospital for vomiting increased with longer duration of erythromycin use (1 week, 2·5 [0·3–25·0]; 2 weeks, 4·3 [1·1–17·2]; >2 weeks, 6·3 [0·8–50·0]), suggesting a possible dose-response effect. Absolute risk of IHPS was 5·1% for infants who took erythromycin for 8–14 days and 10% for infants who took erythromycin for 15–21 days.

The proportions of infants who were male (90 [57·3%] *vs* 77 [61·6%]), white (139 [92·7%] *vs* 106 [87·6%]), and who had been breastfed (101 [64·3%] *vs* 71 [58·7%]) were similar between exposed and unexposed infants. Infants who took erythromycin were less likely to have been born before 36 weeks' gestation (13 [8·3%] *vs* 23 [18·4%]). Reported coughing symptoms from birth to about 1 month of age were more common in erythromycin-exposed infants (32 [20·4%]) than in those who were not exposed (nine [7·2%]). Only four mothers reported erythromycin use while breastfeeding, and none of these women reported any irritability with feeding or vomiting by their infants.

To assess possible risk related to characteristics of erythromycin use, we compared erythromycin use by the seven index IHPS cases with that of the 150 erythromycin-exposed infants who did not develop IHPS. Risk did not differ by erythromycin preparation: four IHPS cases had taken the ethylsuccinate preparation and three had taken the estolate preparation. The seven index IHPS cases were younger at the time erythromycin was started (median 5 days, mean 9·3 days) than the erythromycin-exposed unaffected infants (median 13 days, mean 14·1 days). Erythromycin was started at 1 week or less for 57% of the IHPS cases but for only 28% of the erythromycin-exposed unaffected infants (p=0·11). None of the IHPS cases and 21% of the erythromycin-exposed unaffected infants took erythromycin for less than 10 days (p=0·21).

Discussion

This study suggests a causal role of erythromycin in a cluster of IHPS cases, and raises concerns about the use of erythromycin in neonates.

The first case reports of a possible association between IHPS and erythromycin in five neonates were published in 1976,[8] but the association has remained unconfirmed

and has been thought unlikely.[11] The 1976 study was limited by several factors. It did not compare the five erythromycin-exposed IHPS cases with historical IHPS cases on any factor including erythromycin exposure, and only a modest increase in IHPS frequency was shown. There was also no information on the prevalence of erythromycin use among infants who did not develop IHPS; therefore, the absolute risk of IHPS among erythromycin-exposed infants could not be calculated. The only subsequent report of this association was a single case report of IHPS in a breastfed infant whose mother had taken erythromycin.[9] Previous epidemiological studies of IHPS have not identified erythromycin as a risk factor.

Although IHPS is classified as a birth defect, pyloric muscle hypertrophy is not present at birth among infants eventually developing the disorder.[12] Therefore, postnatal use of erythromycin is not temporally incompatible with development of IHPS.

Our investigation also suggests that cases of IHPS associated with erythromycin differed from historical cases not associated with erythromycin in only a few respects. The index cases had a shorter duration of vomiting before admission to hospital and were less likely to have had projectile vomiting, but they were also younger, on average, at admission than historical cases, and may therefore have received a more aggressive diagnostic investigation and an earlier diagnosis. IHPS progresses over several days from less forceful and infrequent vomiting to more forceful projectile vomiting.[13] Index cases also differed from historical cases in their absence of family history of IHPS, which may reflect an environmental cause for the index cases. The prevalence of a family history of pyloric stenosis (17%) among the 40 historical IHPS cases we reviewed was similar to the 13–14% reported in other regions.[14,15]

Other explanations for our findings must be considered. A diagnostic suspicion bias is not likely because the masked, independent ultrasonography review provided objective confirmation of IHPS diagnosis. The total number of scans reviewed was small, but the 95% CIs for the κ statistic suggest that the agreement was not due to chance alone. Ultrasonography is currently the diagnostic method of choice for IHPS.[14,16–20] There is no evidence from clinical or ultrasonographic findings that the seven index cases were mild or equivocal in comparison with the historical cases.

Moreover, the increase in IHPS does not seem to be due to a community-wide change in the IHPS case definition. An increase in frequency was seen among births at the community hospital, but there were no increases among infants born at other hospitals during this period. The rate of IHPS returned to the lower baseline rate during April and May, 1999. In addition, there were no changes in paediatric surgeons or paediatric radiologists that could account for this increase.

It is also unlikely that the index cases had enlarged pylori that only came to light because of symptoms induced by erythromycin. Comparison of the pyloric muscle of normal children and that of children with IHPS has not found cases of severe hypertrophy among children without symptoms.[21] Furthermore, if the index IHPS cases were infants with subclinical pyloric hypertrophy that was recognised as a result of gastrointestinal side-effects of erythromycin, one would expect them to have less hypertrophy, as measured by pyloric thickness and length, than historical IHPS cases.

The accuracy of erythromycin prescription information was increased by asking mothers to read the information directly from the bottle or to provide the name of the pharmacy for confirmation of prescription details. The prompt investigation of a possible association between erythromycin and IHPS reduced the potential for recall bias. Selection bias was limited by the high participation rate, but may still have occurred to some extent since we did not have the time or resources to contact the families of all infants born at the community hospital during January and February.

The association between erythromycin exposure and IHPS suggests a possible role for motilin receptors. Erythromycin is a motilin agonist[22,23] and induces the activity of migrating motor complexes in the stomach.[24] It specifically increases antral motility[25] and contraction of the pyloric bulb,[26] and is therefore used in low doses to improve gastric emptying.[25,27] The much higher doses that are used for an antibiotic effect can result in strong, non-propagated contractions.[25,27] This marked increase in motility may lead to hypertrophy of the pylorus. The possible involvement of motilin receptors in IHPS is also consistent with the epidemiology of the disorder. Motilin receptors are not functional in infants less than 32 weeks' gestational age, and are not normally functional in term newborn infants.[24] The time course of the development of functional motilin receptors may therefore account for the typical age of onset of IHPS as well as the delayed appearance of IHPS in premature infants.[3–5]

Although the prevention of pertussis in infants is important because most pertussis hospital admissions and deaths occur in babies younger than 1 year of age,[28] our findings indicate that recommendations for erythromycin prophylaxis after pertussis exposure of neonates[10] should be examined further. More information is needed on the effectiveness of antibiotics that are not motilin agonists and that may therefore pose less risk to neonates. Finally, public-health officials should continue to use caution in defining risk groups to avoid unnecessary prophylaxis.

Contributors

All investigators contributed to the conception and design of the study. M A Honein, I M Himelright, B Lee, L Patterson, and S Hall assisted with data collection and chart reviews. M A Honein and L J Paulozzi had primary responsibility for the analysis and interpretation of the data. M A Honein drafted the paper, and all investigators provided critical revisions.

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