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The Association of Erythromycin and Infantile Hypertrophic Pyloric Stenosis

Causal or Coincidental?

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Abstract

The safety profile of erythromycin is notable for the frequent occurrence of intolerable gastrointestinal effects. One of the more serious of these is infantile hypertrophic pyloric stenosis (IHPS). A recent cluster of IHPS cases prompted an epidemiological investigation which identified oral erythromycin chemoprophylaxis of pertussis as the major risk factor. Evidence suggests an association between early postnatal erythromycin exposure and IHPS. There is no substantive evidence of a risk associated with prenatal exposure, with the single published case-control study to date producing negative findings. The epidemiological investigations of the association with early postnatal exposure have reported significantly elevated odds ratios but have a variety of methodological limitations that prevent definitive conclusions being made. Nevertheless, the concordance of findings across studies increases the strength of evidence favouring an association. The prominent gastrokinetic properties of erythromycin have been postulated as the mechanism behind this phenomenon. A comprehensive assessment of this potential adverse effect should consider its biological plausibility in light of known gastrointestinal physiology, its modulation by erythromycin, and the known pathophysiology of IHPS. Gastrointestinal motor activity in the fasted mammal consists of three phases, phase III being large amplitude contractions called migrating motor complexes (MMC) that can be initiated by motilin and erythromycin. The gastrokinetic effects of erythromycin are variable and complex and include effects on the timing, duration, amplitude and distribution of

MMCs. It has been speculated that the motilinomimetic effects of erythromycin on antral smooth muscle function, such as the MMC, may mediate the effect via work hypertrophy. Although intuitively plausible and consistent with hypertrophic obstructive changes similar to IHPS observed in hyperplastic rat ileum after artificially induced mechanical obstruction, there is no direct evidence of this phenomenon. Further complicating the association is the limitations of our knowledge about the pathophysiology of IHPS, including numerous genetic abnormalities, increased parietal cell mass, and gastric hyperacidity. The implications of the reported findings with erythromycin on the benefit-risk profiles of newer macrolides and azalides must be considered. The available data on the comparative gastrokinetic properties of macrolides are significant for the potent gastrokinetic properties and its acid degradation products, the marked variation in gastrokinetic properties associated with macrolide ring size, and the requirement for specific glycosidic linkages at the C-3 and C-5 carbons of the macrolide ring. The variation in gastrokinetic properties associated with variations in molecular structure suggests that if the association between erythromycin and IHPS is causal it may not be a class effect.

Erythromycin has gained widespread use for a variety of indications but its limitations include suboptimal pharmacokinetics necessitating four times daily administration and the frequent occurrence of intolerable gastrointestinal adverse effects, the mechanism of which are not established. One of the more serious gastrointestinal effects that has occasionally been reported with erythromycin is infantile hypertrophic pyloric stenosis (IHPS). The search for newer macrolides was undertaken in the 1980s to obtain compounds with more favourable pharmacokinetics and improved gastrointestinal safety profiles.[1,2]

Erythromycin is recommended as the antimicrobial agent of choice for treatment and prophylaxis of pertussis in infants less than 6 months of age.[3,4] A recent cluster of cases of IHPS prompted a published epidemiological investigation which identified oral erythromycin chemoprophylaxis for pertussis to be the major risk factor.[5] To fully evaluate the nature of this association, consideration must be given to the strength of the evidence linking erythromycin and IHPS and whether the experience with erythromycin can be extrapolated to other macrolides and azalides. This review addresses these questions by providing a comprehensive review and analysis of the following: (i) relevant basic science of gastrointestinal (GI) motility; (ii) relevant basic science and clinical aspects of IHPS; (iii) the limitations of the reported association between erythromycin and IHPS; (iv) the gastrokinetic effects of erythromycin; (v) comparative pharmacology and structure-gastrokinetic activity relationships of macrolides and azalides and whether these data support or refute the extrapolation of the findings with erythromycin to other macrolides and azalides; and (vi) relevant safety experience with the related azalide azithromycin including repeat dose animal toxicology studies, clinical trials in humans, and post-approval adverse event reports with the objective of detecting signals of similar events with a related but chemically and pharmacologically distinct compound.

1. An Overview of Normal Gastrointestinal Motility

There are multiple, distinct GI contractions that vary by location and timing in relation to meals. Forward propagating contractions include the migrating motor complex (MMC), primary oesophageal peristalsis, local reflex peristalsis, and giant peristaltic contractions. Backward propagating contractions are involved in retrograde propulsion as in vomiting.[6,7]

This review will focus on forward propagating gastroduodenal contractions. Gastroduodenal motor activity can be broadly divided into digestive and interdigestive phases. In the digestive phase gastric emptying is marked by highly co-ordinated antral, pyloric and duodenal contractions. Gastrointestinal motor activity in the fasted mammal consists of three phases. Phase I is a period of little or no activity, phase II has intermittent contractions, and, phase III is characterised by large amplitude contractions known as the migrating motor complex (MMC) because they start proximally in the stomach and progress caudally to the terminal ileum. After digested food is transferred into the duodenum any retained food is swept out of the stomach by the MMCs. The MMC is thus said to serve an intestinal 'housekeeping' function.[6,8] Eating interrupts the interdigestive phase with a return to continuous low amplitude contraction.[6,8]

The MMC is cyclical (every 1 to 2 hours) and can be initiated by motilin, somatostatin, prokinetic agents and opioids. Its frequency is set by interstitial cells of Cajal which are non-neuronal, non-myocytic electrical pacemaker cells located between the circular and longitudinal layers of GI smooth muscle.[6,9] The MMC can be studied and characterised in terms of duration, frequency, amplitude and migration velocity of contraction. A frequently cited variable is the motility index that is a function of contraction amplitude multiplied by contraction frequency.

Some of the gastrointestinal adverse effects of macrolides have been attributed to a motilinomimetic mechanism despite the observation that motilin infusions were not associated with similar adverse effects in humans or dogs.[10] A motilinomimetic effect is invoked by Honein et al.[5] as the biological basis of the association between erythromycin and IHPS. Motilin is a 22 amino acid peptide that can induce the MMC in various species.[11] Studies of synthetic truncated peptides and quantitative structure activity relationships indicate that the required pharmacophore is contained in the *N*-terminal portion of the motilin molecule.[12-14]

The human motilin receptor has been cloned and shown to be a 7-transmembrane G-protein coupled receptor.[11] In the upper human gastrointestinal tract the highest concentration of motilin receptors are found in the gastric antrum where they are located on enteric neurons.[11,15] As a cell surface membrane receptor, the effect of a given motilide may be related to its blood concentrations. This cell surface location of the motilin receptor may be relevant given the comparative distributional properties of macrolides and azalides, which will be described later in this review.

2. An Overview of Infantile Hypertrophic Pyloric Stenosis (IHPS)

IHPS is a common cause of protracted vomiting in infants with an incidence that ranges from approximately 1.5 to 4 cases per 1000 live births.[16] The classic full-blown clinical presentation is nonbilious projectile vomiting that occurs after feeding with visible gastric peristaltic waves and a palpable 'olive' in the upper midline abdomen. Metabolic alkalosis is a common complication. Symptoms usually develop at two to eight weeks of age. Although there have been reports of successful medical treatment (e.g. atropine) the standard of care is pyloromyotomy.[16,17] The disorder shows a sex predilection, being two to five times more common in males. Other demographic associations include a higher incidence in Whites and firstborns, as well as, a positive family history.[16,18,19] Clinical diagnosis is often corroborated by abdominal ultrasonography with measurement of pyloric width and length.[20-23] Because of variations of these parameters with bodyweight and overlap between normal infants and those with pylorospasm and IHPS, various ultrasonographic parameters have been proposed such as the pyloric ratio.[24,25] On the basis of ultrasonographic findings some have proposed a threefold diagnostic classification of normal, pylorospasm with early evolving IHPS and IHPS.[26] Of relevance to the current analysis is the identification in some case series of 'non-obstructive hypertrophic pyloric stenosis' in which pyloric length and thickness are

compatible with IHPS but are not accompanied by persistent functional obstruction demonstrated on prolonged real time scanning.[20] In one series this finding was observed in older infants and was attributed to recovering IHPS.[20]

Although generally considered an acquired disorder, congenital/genetic factors are suggested by cases of congenital/neonatal hypertrophic pyloric stenosis,[27-30] occurrence in twins[31] and reported associations with various congenital anomalies including structural urinary tract abnormalities,[32] polyhydramnios,[28] Turner's syndrome,[6] phenylketonuria,[6] trisomy 18,[6] and Smith-Lemli-Opitz syndrome[6,33] and fetal ultrasonographic demonstration of persistent gastric dilation in a case of IHPS.[34] Among 25 patients with hypertrophic pyloric stenosis, an absent or hypoplastic mandibular frenulum was noted in 92% compared with 1.6% of 319 control infants.[35] Familial cases have been localised to specific genetic loci.[36]

The mechanism(s) of IHPS are unknown and it is unclear whether the underlying abnormality is congenital or acquired. There are no confirmed predictive animal models although pyloric hypertrophy has been reported to be induced in dogs by maternal and/or neonatal pentagastrin administration[37] and in rats by perinatal inhibition of nitric oxide synthase or pyloric ligation.[38] The findings in the dogs were reportedly indistinguishable from the human variety of IHPS.[37] Despite the fact that the gastrokinetic effects of macrolides have been most frequently studied and demonstrated in dogs, no published reports have been identified of hypertrophic pyloric stenosis in dogs (or any other animals) from repeat dose toxicology studies with macrolides. There is also no direct evidence that increased antral smooth muscle contraction leads to pyloric stenosis in either animals or humans.

Induction of pyloric stenosis in dogs (with histopathological findings similar to that observed in human IHPS) by pentagastrin infusion is consistent with findings in humans which suggests that a genetic or constitutional increase in parietal cell mass with resulting hyperacidity may be the origin of IHPS.[39] IHPS due to increased parietal cell mass with resulting gastric hyperacidity is a particularly intriguing possibility given the extremely potent gastrokinetic properties of one of the acid breakdown products of erythromycin (8,9-anhydroerythromycin A 6,9-hemiketal) which cannot be formed from the breakdown of certain structurally related agents, such as azithromycin and clarithromycin, in an acid environment.[40,41]

Ultrastructural and biochemical findings observed in IHPS are not limited to smooth muscle hypertrophy and include increased synthesis/expression of collagen, epidermal growth factors, transforming and insulin-like growth factors, absent interstitial cells of Cajal, decreased nerve cell bodies in the myenteric plexus, abnormal innervation of smooth muscle, abnormal nerve and ganglion morphology and diminished neuronal nitric oxide synthase expression.[42-56] It has not been determined which of these findings play a causative role and which are effects of hypertrophic obstruction. Some of the complex ultrastructural changes observed in IHPS have been observed in hyperplastic rat ileum after mechanical obstruction with a circumferential plastic film for 18 to 24 days.[57]

Differential diagnosis includes eosinophilic gastroenteritis, which can mimic IHPS clinically, sonographically, radiologically and at surgery. The coexistence of these two conditions has been reported, so as a result an eosinophilic tissue response to IHPS cannot be ruled out. The correct diagnosis may depend on peripheral blood eosinophilia and/or antral biopsy. The clinical differentiation of these two conditions affects patient management as complete resolution of eosinophilic gastroenteritis has been reported with nonoperative interventions including formula changes and corticosteroids.[58-61]

3. Erythromycin and IHPS

In the last 24 years there have been a total of 40 published cases of IHPS subsequent to erythromycin exposure. Five of these were reported as a case series,[62] seven were reported as a single case reports plus six cases identified through a retrospective chart review,[63] six cases were also identified

through retrospective cohort study,[64] seven cases were reported in the IHPS cluster investigation,[5] and nine were recently identified in another retrospective cohort study.

In the original case series, six infants with IHPS were retrospectively identified from 963 live births between November 1972 and October 1973 in a US military hospital.[62] Five of the six infants had been treated with oral erythromycin estolate 40 mg/kg/day for various skin/soft tissue infections. Four of the five infants were male. In each case symptoms started within 1 to 2 days and a diagnosis of IHPS was made from 1 to 11 days of commencing erythromycin therapy. None of the cases provided information on family history of IHPS, associated congenital anomalies, co-medication use, or complications of pregnancy. The author of this case series noted that the incidence of IHPS in this hospital during the index year was a 3-fold increase from prior years as well as a 2- to 3-fold increase over the national average. Several factors complicate attribution of IHPS to erythromycin in these cases. First, the risk of IHPS subsequent to erythromycin use cannot be determined since the number of infants treated with erythromycin who did not develop IHPS is unknown. The return of the incidence of IHPS to baseline during the following year after erythromycin use in infants was stopped is impossible to interpret since erythromycin use prior to the index year and baseline year-to-year variability in IHPS is not provided. Additionally, the extremely short time interval between the start of erythromycin and diagnosis of IHPS in certain cases (e.g. within 1 day of starting erythromycin) seems improbable given the requirement for significant protein synthesis to result in obstructive muscle hypertrophy and hyperplasia. This suggests that in some of these cases IHPS was already present and predictable erythromycin-induced gastrointestinal adverse effects were the stimulus for clinical evaluation and recognition.

Stang[63] subsequently performed a retrospective chart review of all IHPS cases (n = 122) treated with pyloromyotomy in a single hospital between January 1979 and December 1983. This was prompted by the observation of an infant who developed pyloric stenosis subsequent to possible lactational exposure to erythromycin base (maternal dose of 250mg orally three times daily). Stang[64] stated that 15 of the 122 infants were being treated with medications concurrently at the onset of the vomiting symptoms that led to a diagnosis of pyloric stenosis. Six of these 15 infants (5%) were treated with erythromycin for diagnoses of impetigo, positive staphylococcal nare cultures, periorbital cellulitis, presumed chlamydia pneumonia with conjunctivitis, otitis media, and maternal treatment of mastitis. Aside from the retrospective and uncontrolled nature of these observations it should be noted that by far the most common risk factor was a positive family history of IHPS in a first-degree relative (15.5%). The time delay between starting erythromycin and onset of IHPS was not provided in any of the cases. It cannot be determined if the relative frequency of erythromycin use in IHPS cases merely reflect the relative frequency of erythromycin use compared with other antibiotics in this age range.

A recent publication described an investigation of a cluster of seven IHPS cases identified in the US.[5] This involved a cohort of approximately 200 infants in a single community hospital who received erythromycin for pertussis prophylaxis after a cluster of neonatal pertussis cases was observed. Based on a comparison of the seven index cases with historical cases and a retrospective cohort study, the investigators concluded that erythromycin was causally implicated based on a significantly elevated relative risk that notably displayed a treatment duration response relationship. Attributing causality to erythromycin in this study is complicated by several serious methodological limitations. With respect to the historical comparison, it is no surprise to find all index cases were exposed to erythromycin because using birth cohorts from differing time periods is susceptible to significant 'cohort effects'. Almost all (90.2%) of the index birth cohort was exposed to erythromycin. Indeed, it is likely that for any other arbitrarily

chosen outcome of interest in the index cohort, such as diarrhoea, most of the diarrhoea cases from the index cohort would have been exposed to erythromycin with fewer or no diarrhoea cases from the historical cohorts (when there was not cohort-wide exposure to erythromycin) resulting in a significant association. Therefore, historical comparison is not an appropriate study design to evaluate the association between erythromycin exposure and IHPS. The finding of a significantly higher incidence of IHPS at the hospital in February 1999 compared with the rate for infants born in 1997 and 1998 should also be viewed with circumspection due to the high level of monthly variation in reported baseline rates of IHPS. With respect to the retrospective cohort analysis it is important that the upper limit of the 95% confidence interval (CI) around the point estimate of the relative risk (RR) associated with erythromycin is infinity (95% CI 1.7 to ∞) which is not statistically interpretable due to the small sample size involved. If there was even one case of IHPS among infants not exposed to erythromycin in January 1999 (which is within the observed average incidence of IHPS at the community hospital) the association between erythromycin use and IHPS would not have attained statistical significance (RR = 5.6; 95% CI 0.69 to 44.7). The wide 95% confidence interval indicates that the estimate is unstable.

In a recent epidemiological study by Mahon et al.,[64] of the 14 876 infants that were eligible in their retrospective cohort study conducted from 1993 through 1999, 43 infants developed IHPS. Of the 14 876 infants, 226 of them were prescribed a systemic course of erythromycin within the first 2 weeks of life, and, 469 of them within the first 3 months. Of the six infants who received erythromycin and developed IHPS, all of them developed the symptoms when erythromycin was started during the first 2 weeks of life and treatment was continued for a prolonged period of at least 14 days. Although the relative risk was higher (RR = 10.51; 95% CI 4.5 to 24.7) with systemic forms of erythromycin, topical formulations did not have any associated increased risk in infants. An interesting ancillary finding of the study was that there appeared to be a higher, albeit non-significant, RR of developing IHPS in infants exposed *in utero* during the last 10 weeks of their gestation. Although deserving of more research, this finding is too premature to warrant any changes in clinical practice at this time as it was not replicated in a subsequently published epidemiological study.[65] Shortcomings of this study include issues related to the study's reliance on the data collection system/programme which did not monitor patient compliance, missed out-of-network prescriptions and may have under-recognised documented IHPS due to varying key search words. Like previous reports this study also did not research any familial history of IHPS, but to their credit, the study authors did emphasise the importance of keeping the RR of their findings in perspective. As an example, based on their findings, 42 infants less than 2 weeks of age would have to be treated with systemic erythromycin to identify a single case of IHPS, and, more than 300 mothers would have to be treated with a macrolide during the last 10 weeks of pregnancy to result in a single infant with IHPS, if the findings represent a real causal association.

Other questions and limitations of the above described also exist and merit mention. First, the male sex predilection of the index cases was 86%. This is an interesting finding given the known male sex predilection in IHPS in the absence of erythromycin exposure. If erythromycin-induced smooth muscle contraction leads to IHPS via work hypertrophy it is not clear why this would occur preferentially in males to preserve the known sex predilection if erythromycin was the primary cause of IHPS in these infants. Secondly, a lack of histopathological confirmation to exclude eosinophilic gastroenteritis that may mimic IHPS clinically, sonographically and at surgery. Lastly, the possibility of detection bias. Although the authors claim this is excluded based on comparable pyloric length and thickness between index and control IHPS cases, the significantly lower incidence of projectile vomiting in the index cases could reflect increased parental vigilance or sensitivity to signs

of illness as well as predictable erythromycin-associated adverse effects resulting in increased detection of nonobstructive hypertrophic pyloric stenosis in certain cases.

The latest analysis of this association was a large retrospective cohort study design applied to the Tennessee Medicaid population.[66] The base population consisted of all children born in Tennessee between 1985 and 1997, with complete information in the Tennessee birth certificate files, who were discharged from the birth hospital and enrolled in Medicaid by 3 days of life (n = 314 029). Cases of IHPS hospitalised between 3 and 90 days of life were extracted from this population based on the dual criteria of having a hospital discharge diagnosis of pyloric stenosis and an associated procedural code for pyloromyotomy. Outpatient prescription files of all children in the base population were searched to locate prescriptions for erythromycin between 3 days of life and the date of hospitalisation (IHPS cases) or 90 days of life (controls). Among the 314 029 Medicaid-enrolled births there were 804 infants meeting the study criteria for IHPS (2.6 of 1000 infants) and 7138 infants with a filled prescription for erythromycin (2.3%). Of the 804 infants meeting study criteria for lHPS, nine were exposed to erythromycin up to postnatal day 90. Exposure to erythromycin prior to 90 days of life was associated with an adjusted incidence rate ratio of 2.05 (95% CI of 1.06 to 3.97). This increased risk was essentially related to very early erythromycin exposure. Exposure to erythromycin between 3 and 13 days of life was associated with a significantly increased incidence rate ratio of 7.88 (95% CI of 1.97 to 31.57) whereas the risk was not significantly increased by erythromycin exposure after 14 days of life. The strengths of this study included the size of the population base and the dual criteria for identifying cases. Limitations included the uncertain potential influence of family history of IHPS, inpatient prescriptions, and potential dose/duration response relationships as well as unconfirmed drug exposures and the wide confidence interval for very early erythromycin exposure.

Because the recent investigations of neonatal erythromycin exposure raised a concern about a possible risk associated with erythromycin use in late pregnancy, the Slone Epidemiology Unit (SEU) recently published results of an epidemiological analysis.[65] Since 1976 the SEU had screened for signals of drug-induced fetal malformations by applying case-control methodology. Briefly, infants born with congenital malformations were identified by review of hospital logs, surgical logs, and clinic or office records of participating hospitals in several metropolitan areas. The emphasis was on major defects identified within 5 months of birth. Infants with no malformations were enrolled to provide controls. Diagnoses were confirmed by review of medical records. Using detailed structured interviews, exposure information was obtained by trained nurse-interviewers. Information was elicited on exposures commencing prior to pregnancy throughout gestation. These databases are screened annually by estimating odds ratios for all drugs and drug classes for each adverse event, compared with all other events. Crude and Mantel-Haenszel adjusted odds ratios are calculated. Using infants with no malformations and those with other malformations, the SEU found no increased risk associated with gestational erythromycin exposure regardless of timing of exposure. While this result is reassuring from the perspective of gestational exposure, the completeness of case ascertainment is a significant factor since IHPS typically occurs at 2 to 8 weeks of age and may not have always been recorded or detected in a search of congenital abnormalities. Furthermore these findings cannot be extrapolated to neonatal exposure given the uncertain knowledge of the underlying exposure levels.

4. Gastrokinetic Effects of Erythromycin

Discussing the gastrokinetic properties of erythromycin is useful when evaluating the association of erythromycin and IHPS and the proposed motilinomimetic mechanism.

A variety of gastrointestinal adverse effects are expected with both intravenous and oral erythro-

mycin including nausea, vomiting, epigastric pain and diarrhoea. One of the objectives of developing newer macrolides and azalides was to improve gastrointestinal tolerability. *In vitro* and *in vivo* studies with rabbits, dogs and humans have provided potential mechanisms for these adverse effects although as stated above motilin infusions did not cause gastrointestinal adverse events in dogs or humans.[10,67-69]

Although erythromycin was originally reported to stimulate the release of motilin, binding to motilin receptors has more recently been invoked to explain the propensity of erythromycin to cause adverse gastrointestinal adverse effects, despite the fact that infusions of motilin were not associated with gastrointestinal adverse effects.[7,10] Erythromycin has been shown to have the same regional and species specificity as motilin.[10] Erythromycin displaces motilin from antral muscle tissue in rabbits, cats and humans.[7,10] Muscle strips or intestinal segments of rat and dog do not demonstrate a contractile response to erythromycin but human, feline, and rabbit preparations do.[10] This may be explained in part by trans-species differences in motilin receptor distribution (i.e. neuronal versus smooth muscle cell localisation).[10,11] Parts of the erythromycin molecule including carbons 1-9 and the dimethylglucosamine may be structurally similar to the motilin pharmacophore.[7,10,12-14]

The gastrointestinal motor effects of erythromycin are variable and complex and may be partly reduced by atropine in dogs.[7,8] In dogs it can induce premature MMCs, retrograde giant contractions, and amyogenesia.[7] It also causes dose-dependent changes in MMC velocity and cycle length.[7] This discussion will focus on antroduodenal motor effects.

In 1984 two groups independently described smooth muscle contractile effects of erythromycin in the small intestine of dogs.[10] Erythromycin was shown to induce a pattern of smooth muscle contraction originating in the stomach with a duration and migration velocity that was the same as the spontaneous interdigestive MMC.[10] Gastrokinetic effects of erythromycin in the fasting dog were dose and route-dependent. Low oral doses (1 mg/kg) induced premature MMCs with decreased cycle length and migration velocity over the entire intestine. Intermediate oral doses (10 mg/kg) did not induce a premature MMC but were associated with decreased cycle length and migration velocity. High oral doses (25 mg/kg) did not induce premature MMCs but were associated with a prolonged MMC cycle length and decreased migration velocity. Intravenous erythromycin interrupted MMCs in progress but doses of 10 mg/kg were associated with duodenal clustered contractions, which were similar to proximal interdigestive contractions in the proximal duodenum, but were much longer in duration and not associated with MMCs. Oral erythromycin was also associated with clustered duodenal contractions. Significantly increased motility indexes in the gastric antrum of dogs have been observed in the postprandial state after administration of 200mg of oral erythromycin.[7] The time course of these effects varied by route and formulation with intravenous erythromycin inducing antral and duodenal contractions within one minute of the start of the infusion. A variable time lag was observed between administration of oral erythromycin before onset of clustered duodenal contractions and the incidence of these contractions was greater after erythromycin stearate than with erythromycin ethylsuccinate at all doses.[7] The duration of these contractions did not vary by route of administration.[7] Considering formulation specific differences in pharmacokinetics this may indicate that the incidence of these contractions may be related to serum drug concentrations.

Erythromycin is also a gastrokinetic agent in humans with the specific pattern of induced gastrointestinal motor activity being a function of fasted versus postprandial administration and administered dose. Low dose (1 mg/kg/h and 3 mg/kg/h) intravenous erythromycin induced premature MMCs in fasted healthy adults that were of comparable amplitude, frequency, and velocity as naturally occurring MMCs but of longer duration.

Erythromycin 200mg given intravenously significantly increased the amplitude of postprandial antral contractions although the number of contractions was not increased. Another finding was that the antral contractions could be manometrically recorded higher up in the stomach.[67-69]

Because of its potent gastrokinetic properties erythromycin has been studied in the treatment of various gastrointestinal motility disorders and feeding intolerance in low birthweight and premature infants. Some studies administered antimicrobial doses of erythromycin for over 2 weeks. Erythromycin appeared well tolerated and no reports of IHPS originating from these studies were identified. Of course pre-existing dysmotility disorders or feeding intolerance in these infants could be associated with a decreased baseline risk of IHPS and the small number of infants involved indicate limited power of such trials to detect such an event.[70-73]

5. Structure-Activity Relationships and Comparative Pharmacokinetics of Macrolides and Azalides

Abundant data on the structure-gastrokinetic activity relationships of macrolides, mostly involving 14- and 16-member ring macrolides, e.g. clarithromycin and midecamycin, may explain the lower incidence of gastrointestinal adverse effects observed with azithromycin and certain related macrolides, e.g. clarithromycin and roxithromycin, relative to erythromycin.[74-82] Some gastrokinetic effects of erythromycin are motilin-receptor mediated but other mechanisms are operative as well.[7,10] A motilinomimetic mechanism was proposed by Honein et al.[5] to explain how erythromycin could cause IHPS. Structure-gastrokinetic activity relationships, comparative motilin receptor binding studies and comparative pharmacokinetics suggest that findings with erythromycin may not be generalisable to all macrolides and azalides. Macrolide structure-gastrokinetic activity relationships have been explored under various experimental conditions. Test systems have included isolated rabbit gastric antral smooth muscle strips in tissue baths (motilin receptor binding and contractile response studies), dogs (conscious and anaesthetised, fasting and fed), and humans. The majority of *in vivo* studies used intravenous administration. Surgically implanted serosal strain gauge force transducers were generally used in animal systems while side-opening manometric probes were usually used in humans.[74-82]

Several findings have emerged from these studies, including: (i) in a comparison of multiple 14-member ring macrolides in current clinical use, erythromycin demonstrated the greatest gastrokinetic potency in both the fasting and fed canines;[81] (ii) 8,9-anhydroerythromycin A 6,9-hemiketal, one of the natural acid decomposition products of erythromycin, was many times more potent than erythromycin in terms of *in vivo* smooth muscle contractility and motilin receptor binding *in vitro* and *in vivo* animal systems;[74,77] (iii) the most potent synthetic gastrokinetic macrolides did not have antimicrobial activity and were derivatives of 8,9-anhydroerythromycin A 6,9-hemiketal;[83,84] (iv) ring size was important with 14-member macrolides showing motilin receptor binding and gastrokinetic activity but 16-ring members being inactive in the same assays as well as in humans;[75,77,79-82] and (v) a dimethylamino sugar and a neutral sugar attached at C-3 and C-5 in a parallel glycosidic linkage appears to be a structural requirement. [10,74,76]

Unlike erythromycin, which is not stable in the acidic environment of the stomach, where it can decompose to the potent motilinomimetic 8,9-anhydroerythromycin A 6,9-hemiketal, certain related agents such as azithromycin and clarithromycin are acid stable. In the case of azithromycin the expanded 15-member azalide ring prevents the intramolecular cyclisation reaction necessary to form the strongly gastrokinetic hemiketal.[40,41] Although the formation of the potent gastrokinetic hemiketal decomposition product of erythromycin may be partially mitigated by the lower neonatal gastric acidity compared with the adult, gastric retention times are also longer in the neonate. Also, infants predisposed or destined to develop IHPS

may have increased parietal cell mass and gastric hyperacidity.[39] Therefore oral erythromycin administration could expose the infantile gastric antrum to the potent gastrokinetic erythromycin hemiketals that would not occur with azithromycin or other macrolides. Intravenous erythromycin could also result in a similar exposure since intravenous erythromycin appears in the gastric juice within minutes of injection.[10]

While the vast majority of studies have examined 14- and 16-member ring macrolides, a few published studies looked specifically at the comparative motilinomimetic and gastrokinetic activity of the 15-member ring azithromycin.[78,80] One published study cited unpublished data showing that azithromycin had potency almost equal to erythromycin in displacing receptor-bound motilin (7.33 and 7.24, respectively) in rabbit antral smooth muscle although no further details were provided.[80] Another relevant study using intravenous azithromycin 4 mg/kg showed that this agent had motilin receptor binding properties and contractile effects in rabbits and dogs that were comparable to equal doses of erythromycin and significantly greater than equal doses of clarithromycin.[78] However, several features of this study complicate its interpretation. It was the only study identified that was carried out under anaesthesia, apparently at the time of surgical implantation of serosal force transducers. It was not placebo controlled, with erythromycin used as a control. The brief manuscript did not provide the number of animals or the number or sequence of treatment arms. Methodological questions aside, the clinical relevance of these findings is uncertain given the lower doses and blood concentrations of azithromycin compared with erythromycin with conventional administration.

Of interest is a study which compared the effect of azithromycin, the 16-member ring macrolide midecamycin (16-member rings have little or no gastrokinetic effects) and placebo on several antral motility indices in 11 healthy volunteers. Interdigestive antral MMC cycle length, number of phase III activity fronts per hour, and the duration of phase III with azithromycin were not significantly different from placebo or midecamycin. The only statistically significant interdigestive difference found was an increase in the number of phase III contractions originating in the stomach. In the postprandial period, the number of proximal and distal antral contractions with azithromycin was not significantly different from placebo or midecamycin. The proximal and distal gastric motility indices were significantly higher with azithromycin than with midecamycin or placebo.[80]

Finally, erythromycin and related antibiotics such as azithromycin demonstrate markedly different administration regimens and pharmacokinetics that may be relevant to this analysis. As an example, erythromycin administration involves much higher molar quantities and blood drug concentrations than azithromycin. The blood concentration attained may be important for a pharmacodynamic effect mediated by a cell surface receptor such as the motilin receptor. Certain gastrokinetic effects of erythromycin in dogs and humans have in fact been correlated with concentration of drug in blood.[7,85] Erythromycin undergoes extensive hepatic metabolism. Whether cases of IHPS were correlated with pharmacokinetic variability in neonatal erythromycin metabolism is impossible to say since the observational findings of cases of IHPS did not involve measurement of erythromycin blood levels.

Finally, extensive toxicological studies have been performed with azithromycin in laboratory animals including acute, subacute, and chronic (6 months duration) toxicity studies in neonatal and adult dogs and rats.[86] Maximum treatment dosage and duration in these toxicology studies was 40 mg/kg/day by oral gavage for 17 days in neonatal rats, 60 mg/kg/day by oral gavage for 1 month in neonatal dogs, 20 mg/kg/day intravenously in adult rats, 20 mg/kg/day intravenously for 6 months in adult rats, 20 mg/kg/day intravenously in adult dogs for 1 month, 30 to100 mg/kg/day intravenously for 6 months in adult dogs, and 30 to100 mg/kg/day (alternating cycles of 10 days of treatment and 10 days of no treatment) by oral gavage

for 6 months in adult dogs. There were no cases of hypertrophic pyloric stenosis detected on gross necropsy. No effect of azithromycin was noted in gastric motility studies in rats.

6. Study of Azithromycin Manufacturer's Safety Database

Manufacturers of microlides were requested by regulatory authorities to perform an analysis of their product safety databases to ascertain if compounds structurally related to erythromycin were also associated with IHPS.

The early alert safety database of the manufacturer of azithromycin contains spontaneous adverse event reports, adverse events reported from registries, reports of adverse events published in the medical literature, and reports of serious adverse events reported from clinical studies regardless of causality. A sensitive case search and retrieval strategy designed to account for possible adverse event coding variability was used in thhe requested analysis. The database was searched for case reports coded with the WHO Adverse Reaction Terminology (WHO-ART) preferred adverse event terms 'intestinal obstruction' and 'pyloric stenosis' entered onto the database up to August 1, 2000. A database search with these WHO-ART preferred terms would also capture case reports with the adverse event codes 'infantile hypertrophic pyloric stenosis', 'acquired hypertrophic pyloric stenosis', and 'hypertrophic pyloric stenosis'. The database was also searched for any case reports with adverse event codes potentially representing surgical intervention for IHPS. There were 13 388 azithromycin adverse event reports entered into the database up to August 1, 2000. Of these 13 388 case reports, 15 involved infants who were 2 months old or younger, none of which involved IHPS. There were no reports of IHPS irrespective of age eliminating the possibility of relevant reports in which age was either wrongly entered into the database or unknown. There was one report of a 31-year-old male with unknown medical history who experienced fatal cryptosporidiosis and acquired hypertrophic pyloric stenosis. Given the fact that the patient was also treated with ritonavir and the known association of AIDS-associated cryptosporidiosis with gastric antral inflammation, stricturing and stenosis, the pyloric stenosis is considered to represent the natural history/complications of the cryptosporidiosis and is unrelated to azithromycin.[87-89]

In addition to the database search, a search of the literature did not identify any published clinical trials of azithromycin treatment/prophylaxis of pertussis in infants less than two months of age. Two published trials involved infants and young children and included a very small number of infants in the age range of interest but these did not report any adverse events.[90,91]

7. Summary and Conclusions

The association of erythromycin usage in infants with IHPS is an important signal that warrants continued surveillance. Like many signals in drug safety there are serious limitations to the data with residual uncertainty as to whether the association represents a real effect, residual confounding, the play of chance or any combination of the above. Associations of adverse events with drugs do not always hold up under formal epidemiological study as was observed with IHPS and maternal use of benedectin.[92,93] Nevertheless, the concordance of findings among the cited epidemiological studies of neonatal exposure to erythromycin increases the weight of evidence in support of an association.

A crucial question is whether the uncertain findings with erythromycin can be extrapolated to other macrolides and azalides given that structural variations among these compounds affect their gastrokinetic properties. The differential physicochemical characteristics of erythromycin are also pertinent since it undergoes acid catalysed decomposition into a potent gastrokinetic hemiketal that cannot occur with the 15-member ring of azithromycin and other macrolides. Some gastrokinetic properties of erythromycin were correlated with drug concentrations in the blood so the much lower blood levels achieved with conventional

azithromycin administration could be an important differential factor. However, this would not explain the lack of reports of IHPS with other macrolides with equal or higher blood levels such as clarithromycin and roxithromycin. Comparative motilin receptor binding and antral smooth muscle contraction studies involving erythromycin versus azithromycin and other macrolides are extremely limited.

The mechanism of IHPS is not established. While the hypothesis that increased antral smooth muscle contraction leads to pyloric stenosis via work hypertrophy and/or hyperplasia is intuitively appealing there is no confirmatory evidence of this in animals or humans. There is indirect evidence for other pathophysiological mechanisms such as genetically or constitutionally increased parietal cell mass and hyperacidity.[32] Such a mechanism could interact additively or synergistically with erythromycin via an erythromycin-specific acid breakdown product (hemiketal) that is the most potent of the naturally occurring motilides.

No cases of IHPS or related disorders have been observed with azithromycin in repeat- dose toxicology studies, clinical trials or post-approval safety surveillance. This could reflect the level of use in the relevant age cohort, absent or decreased risk of IHPS with azithromycin or a combination of these factors. However given the background incidence of IHPS and the relative risk reported by Honein et al.,[5] an event occurring with the proposed frequency should in principle be detectable fairly early in the lifetime of a drug although many factors complicate the generation of drug-adverse event associations.

Given the above referenced limitations of the important safety signal involving erythromycin and IHPS, and the pharmacological, physicochemical, and gastrokinetic variations among macrolides and azalides, any generalisation to the entire class of macrolides and azalides is not supported by the data reviewed.

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References

1. Bahal N, Nahata MC. The new acrolide antibiotics: azithromycin, clarithromycin, dirithromycin, and roxithromycin. Ann Pharmacother 1992; 26: 46-55
2. Rapp R. Pharmacokinetics and pharmacodynamics of intravenous and oral azithromycin: enhanced tissue activity and minimal drug interactions. Ann Pharmacother 1998; 32: 785-93
3. American Academy of Pediatrics Red Book 2000: 435-48
4. Patamasucon P, Kaojarern S, Kusmiesz H. Pharmacokinetics of erythromycin ethylsuccinate and estolate in infants under 4 months of age. Antimicrob Agents Chemother 1981; 19 (5): 736-9
5. Honein MA, Paulozzi LJ, Himelright IM, et al. Infantile hypertrophic pyloric stenosis after pertussis prophylaxis with erythromycin: a case review and cohort study. Lancet 1999; 354: 2101-5
6. Goyal RK, Hirano I. Mechanisms of disease: the enteric nervous system. N Engl J Med 1996; 334 (17): 1106-15
7. Otterson MF, Sarna SK. Gastrointestinal motor effects of erythromycin. Am J Physiol 1990; 259 (22): G355-63
8. Pilot MA, Qin XY. Macrolides and gastrointestinal motility. J Antimicrob Chemother 1988; 22 Suppl. B: 201-6
9. Hirst G, David S. Physiology: a calcium window to the gut. Nature 1999; 399 (6731): 16-7
10. Peeters TL. Erythromycin and other macrolides as prokinetic agents. Gastroenterology 1993; 105: 1886-99
11. Feighner SD, Tan CP, McKee KK. Receptor for motilin identified in the human gastrointestinal system. Science 1999; 284 (5423): 2184-8
12. Khiat A, Boulanger Y. Identification of the motilide pharmacophore using quantitative structure-activity relationships. J. Pept Res 1998; 52 (4): 321-8
13. Haramura M, Tsuzuki K, Okamachi A. Structure-activity of intact porcine motilin. Chem Pharm Bull (Tokyo) 1999; 47 (11): 1555-9
14. Miller P, Gagnon D, Dickner M. Structure-function studies of motilin analogues. Peptides 1995; 16 (1): 11-8
15. Miller P, Roy A, St-Piere S, et al. Motilin receptors in the human antrum. Am J Physiol 2000; 278 (1): 618-23
16. Lund D, Compton C. Weekly clinicopathological exercises: case 26-1999: a three-week-old girl with pyloric stenosis and an unexpected operative finding. N Engl J Med 1999; 341 (9): 679-84
17. Yamataka A, Tsukada K, Yokoyama-Laws Y, et al. Pyloromyotomy versus atropine sulfate for infantile hypertrophic pyloric stenosis. J Pediatr Surg 2000; 35 (2): 338-41
18. Schechter R, Torfs CP, Bateson TF. The epidemiology of infantile hypertrophic pyloric stenosis. Paediatr Perinat Epidemiol 1997; 11 (4): 407-27
19. Applegate MS, Druschel CM. The epidemiology of infantile hypertrophic pyloric stenosis in New York State 1983 to 1990. Arch Pediatr Adolesc Med 1995; 149: 1123-9

20. Stunden RJ, LeQuesne GW, Little KET. The improved ultrasound diagnosis of hypertrophic pyloric stenosis. Pediatr Radiol 1986; 16: 200-5
21. Hallam D, Hansen B, Bodker B, et al. Pyloric size in normal infants and in infants suspected of having hypertrophic pyloric stenosis. Acta Radiol 1995; 36: 261-4
22. Neilson D, Hollman AS. The ultrasonic diagnosis of infantile hypertrophic pyloric stenosis: technique and accuracy. Clin Radiol 1994; 49: 246-7
23. Van der Schouw JT, Van der Velden MTW, Hitge-Boetes C, et al. Diagnosis of hypertrophic pyloric stenosis: value of sonography when used in conjunction with clinical findings and laboratory data. Am J Roentgenol 1994; 163: 905-9
24. Cohen HL, Zinn HL, Haller JO. Ultrasonography of pylorospasm: findings may simulate kypertrophic pyloric stenosis. J Ultrasound Med 1998; 17: 705-11
25. Lowe LH, Banks WJ, Shyr Y. Pyloric ratio: efficacy in the diagnosis of hypertrophic pyloric stenosis. J Ultrasound Med 1999; 18: 773-7
26. Hernanz-Schulman M, Sells LL, Ambrosino MM, et al. Hypertrophic pyloric stenosis in the infant without a palpable olive: accuracy of sonographic diagnosis. Pediatr Radiol 1994; 193: 771-6
27. Hatiboglu MC, Dindar H, Cakmak M, et al. Neonatal hypetrophic pyloric stenosis: congenital or infantile? Tokai J Exp Clin Med 1996; 21 (4-6): 203-5
28. Houben CH, Kiely EM. Congenital hypertrophic pyloric stenosis with associated polyhydramnios in a premature infant. Eur J Pediatr Surg 1997; 7 (3): 184-5
29. Ali KI, Haddad MJ. Early infantile hypertrophic pyloric stenosis: surgery at 26 hours of age. Eur J Pediatr Surg 1996; 6 (4): 233-4
30. Sinha CK, Gangopadhyay AN, Sahoo SP, et al. Congenital hypertrophic pyloric stenosis at birth. Indian J Pediatr 1996; 63 (3): 413-4
31. Zajadacz B, Baraniak A, Juszkiewicz A. Hypetrophic pyloric stenosis in twins. Wiad Lek 1999; 52 (11-12): 616-8
32. Bidair M, Kalota SJ, Kaplan GW. Infantile hypertrophic pyloric stenosis and hydronephrosis: is there an association? J Urol 1993; 150 (1): 153-5
33. Nowaczyk MJM, Whelan DT, Heshka T, et al. Smith-Lemli-Opitz syndrome: a treatable inherited error of metabolism causing mental retardation. CMAJ 1999; 161 (2): 165-70
34. Katz S, Basel D, Branski D. Prenatal gastric dilatation and infantile hypertrophic pyloric stenosis. J Pediatr Surg 1988; 23 (11): 1021-2
35. De Felice C, Di Maggio G, Zagordo L, et al. Hypoplastic or absent mandibular frenulum: a new predictive sign of infantile hypertrophic pyloric stenosis. J Pediatr 2000; 136: 408-10
36. Maraschio P, Maserati E, Seghezzi L, et al. Involvement of the 9q22.1-31.3 region in pyloric stenosis. Clin Genet 1998; 54 (2): 159-60
37. Dodge JA, Karim AA. Induction of pyloric hypertrophy by penatgastrin: an animal model for infantile hypertrophic pyloric stenosis. Gut 1976; 17 (4): 280-4
38. Chen D, Zhao CM, Nylander AG, et al. Trophic effects in the acid-producing part of the rat stomach after pyloric stenosis. Scand J Gastroenterol 1995; 30 (12): 1147-52
39. Rogers IM. The enigma of pyloric stenosis: some thoughts on the aetiology. Acta Paediatr 1997; 87: 6-9
40. Fiese EF, Steffen SH. Comparison of the acid stability of azithromycin and erythromycin A. J Antimicrob Chemother 1990; 25 Suppl. A: 39-47
41. Kirst HA, Sides GD. New Directions for macrolide antibiotics: structural modifications and in vitro activity. Antimicrob Agents Chemother 1989; 33 (9): 1413-8
42. Milla PJ. Gastric outlet obstruction in children. New Engl J Med 1992; 327 (8): 558-9
43. Gentile C, Romeo C, Impellizzeri P, et al. A possible role of the plasmalemmal cytoskeleton, nitric oxide synthase, and innervation in infantile hypertrophic pyloric stenosis: a confocal laser scanning microscopic study. Pediatr Surg Int 1998; 14 (1-2): 45-50
44. Shinohara K, Shimizu T, Igarashi J, et al. Correlation of prostaglandin E2 production and gastric acid secretion in infants with infantile hypertrophic pyloric stenosis. J Pediatr Surg 1998; 33 (10): 1483-5
45. Langer JC, Berezin I, Daniel EE. Hypertrophic pyloric stenosis: ultrastructural abnormalities of enteric nerves and the interstitial cells of Cajal. J Pediatr Surg 1995; 30 (11): 1535-43
46. Shima H, Ohshiro K, Puri P. Increased local synthesis of epidermal growth factors in infantile hypertrophic pyloric stenosis. Pediatr Res 2000; 47 (2): 201-7
47. Shima H, Puri P. Increased expression of transforming growth factor-alpha in infantile hypertrophic pyloric stenosis. Pediatr Surg Int 1999; 15 (3-4): 198-200
48. Oue T, Puri P. Smooth muscle cell hypertrophy versus hyperplasia in infantile hypertrophic pyloric stenosis. Pediatr Res 1999; 45 (6): 853-7
49. Abel RM, Bishop AE, Dore CJ, et al. A quantitative study of the morphological and histochemical changes within the nerves and muscle in infantile hypertrophic pyloric stenosis. J Pediatr Surg 1998; 33 (5): 682-7
50. Oshiro K, Puri P. Increased insulin-like growth factor-I mRNA expression in pyloric muscle in infantile hypertrophic pyloric stenosis. Pediatr Surg Int 1998; 13 (4): 253-5
51. Miyazaki E, Yamataka T, Ohshiro K, et al. Active collagen synthesis in infantile hypertrophic pyloric stenosis. Pediatr Surg Int 1998; 13 (4): 237-9
52. Ohshiro K, Puri P. Increased insulin-like growth factor and platelet derived growth factor system in the pyloric muscle in infantile hypertrophic pyloric stenosis. J Pediatr Surg 1998; 33 (2): 378-81
53. Oshiro K, Puri P. Pathogenesis of Infantile hypertrophic pyloric stenosis: recent progress. Pediatr Surg Int 1998; 13 (4): 243-52
54. Kusafuka T, Puri P. Altered messenger RNA expression of the neuronal nitric oxide synthase gene in infantile hypertrophic pyloric stenosis. Pediatr Surg Int 1997; 12 (8): 576-9
55. Kobayashi H, Wester T, Puri P. Age-related changes in innervation in hypertrophic pyloric stenosis. J Pediatr Surg 1997; 32 (12): 1704-7
56. Vanderwinden JM, Mailleux P, Schiffman SN, et al. Nitric oxide synthase activity in infantile pyloric stenosis. N Engl J Med 1992; 327: 511-5
57. Ekblad E, Sjuve R, Arner A. Enteric neuronal plasticity and a reduced number of interstitial cells of Cajal in hypertrophic rat ileum. Gut 1998; 42 (6): 836-44
58. Hummer-Ehret BH, Rohrschneider WK, Oleszcuk-Raschke K, et al. Eosinophilic gastroenteritis mimicking idiopathic hypertrophic pyloric stenosis. Pediatr Radiol 1998; 28: 711-3
59. Blankenberg FG, Parker BR, Sibley E, et al. Evolving asymmetric hypertrophic pyloric stenosis associated with histological evidence of eosinophilic gastroenteritis. Pediatr Radiol 1995; 25: 310-1
60. Snyder JD, Rosenblum N, Wershil B, et al. Pyloric stenosis and eosinophilic gastroenteritis in infants. J Pediatr Gastroenterol Nutr 1987; 6: 543-7
61. Khan S, Orenstein SR. Eosinophilic gastroenteritis masquerading as pyloric stenosis. Clin Pediatr 2000; 39: 55-7
62. SanFilipo JA. Infantile hypertrophic pyloric stenosis related to ingestion of erythromycin estolate: a report of 5 cases. J Pediatr Surg 1976; 11: 177-80

63. Stang H. Pyloric stenosis associated with erythromycin ingested through breastmilk. Minn Med 1986; 69: 669-70, 682
64. Mahon BE, Rosenman MB, Kleiman MB. Maternal and infant use of erythromycin and other macrolide antibiotics as risk factors for infantile hypertrophic pyloric stenosis. J Pediatr 2001; 139: 380-4
65. Louik CL, Martha M, Mitchell AA. Erythromycin use during pregnancy in relation to pyloric stenosis. Am J Obstet Gynecol 2002; 186: 288-90
66. Cooper WO, Griffin MR, Arbogast P, et al. Very early exposure to erythromycin and infantile hypertrophic pyloric stenosis. Arch Pediatr Adolesc Med 2002; 156: 647-50
67. Tomomsa T, Kuroume T, Arai H, et al. Erythromycin induces migrating motor complex in human gastrointestinal tract. Dig Dis Sci 1986; 31 (2): 157-61
68. Annese V, Janssens J, Vantrappen G, et al. Erythromycin accelerates gastric emptying by inducing antral contractions and improved gastroduodenal coordination. Gastroenterology 1992; 102: 823-8
69. Des Varannes SB, Parys V, Ropert A. Erythromycin enhances fasting and postprandial proximal gastric tone in humans. Gastroenterology 1995; 109: 32-9
70. Ng E, Shah V. Erythromycin for feeding intolerance in preterm infants. Available in The Cochrane Library [database on disk and CD ROM]. Updated quarterly. The Cochrane Collaboration; issue 4. Oxford: Update Software 2000; 2: CD001815
71. Ng PC, Fok TF, Lee CH, et al. Erythromycin treatment for gastrointestinal dysmotility in preterm infants. J Pediatr Child Health 1997; 33 (2): 148-50
72. Simkiss DE, Adams IP, Myrdal U, et al. Erythromycin in neonatal postoperative intestinal dysmotility. Arch Dis Child 1994; 71 (2): F128-9
73. Kubota M, Nakamura T, Mokura T, et al. Erythromycin improves gastrointestinal motility in extremely low birthweight infants. Acta Pediatr Jpn 1994; 36 (2): 198-201
74. Depoortere I, Peeters TL, Matthijs G, et al. Structure-activity relation of erythromycin-related macrolides in inducing contractions and in displacing bound motilin in rabbit duodenum. J Gastrointest Motil 1989; 1: 150-9
75. Itoh Z, Tomoaki S, Nakaya M, et al. Gastrointestinal motor-stimulating activity of macrolide antibiotics and analysis of their side effects on the canine gut. Antimicrob Agents Chemother 1984; 26: 863-9
76. Itoh Z, Suzuki T, Nakaya M, et al. Structure-activity relation among macrolide antibiotics in initiation of interdigestive migrating contractions in the canine gastrointestinal tract. Am J Physiol 1985; 248: G320-5
77. Omura S, Tsuzuki K, Sunazuka T, et al. Macrolides with gastrointestinal motor stimulating activity. J Med Chem 1987; 30 (11): 1941-3
78. Nellans HN, Peeters TL, Petersen AC. Stimulation of gastrokinetic motility: clarithromycin less potent than azithromycin. Proceedings of the 17th International Congress of Chemotherapy; 1991 Jun 24; Berlin. Munich: Futuramed, 1991: 2286-7
79. Sifrim D, Janssens J, Vantrappen G. Comparison of the effects of midecamycin acetate and clarithromycin on gastrointestinal motility in man. Drugs Exp Clin Res 1992; 18 (8): 337-42
80. Sifrim D, Matsuo H, Janssens J, et al. Comparison of the effects of midecamycin acetate and azithromycin on gastrointestinal motility in man. Drugs Exp Clin Res 1994; 20 (3): 121-6
81. Nakayoshi T, Izumi M, Tatsuta K. Effects of macrolide antibiotics on gastrointestinal motility in fasting and digestive states. Drugs Exp Clin Res 1992; 18 (4): 103-9
82. Nakayoshi T, Izumi M, Shinkai S, et al. Comparative study on effects of 14- and 16-membered macrolides on gastrointestinal motility in unanaesthetized dogs. Drugs Exp Clin Res 1988; 14 (5): 319-25
83. Tsuzuki K, Sunazuka T, Marui S, et al. Motilides, macrolides with gastrointestinal motor activity. I. O-substituted and tertiary N-substituted derivatives of 8,9-anhydroerythromycin A 6,9-hemiacetal. Chem Pharm Bull (Tokyo) 1989; 37 (10): 2687-700
84. Sunazuka T, Tsuzuki K, Marui S, et al. Motilides, macrolides with gastrointestinal motor stimulating activity: II. quaternary N-substituted derivatives of 8,9-anhydroerythromycin A 6,9-hemiacetal and 9,9-dihydroerythromycin A. Chem Pharm Bull (Tokyo) 1989; 37 (10): 2701-9
85. Ehrenpreis ED, Zaitman D, Nellans H. Which form of erythromycin should be used to treat gastroparesis? a pharmacokinetic analysis. Aliment Pharmacol Ther 1998; 12: 373-6
86. Data on file, Pfizer Inc.
87. Forester G, Sidhom O, Nahass R, et al. AIDS-associated cryptosporidiosis with gastric stricture and a therapeutic response to paromycin. Am J Gastroenterol 1994; 89 (7): 1096-8
88. Garone MA, Winston BJ, Lewis JH. Cryptosporidiosis of the stomach. Am J Gastroenenterol 1986; 81 (6): 465-70
89. Moon A, Spivak W, Brandt LJ. Cryptosporidium-induced gastric outlet obstruction in a child with congenital HIV infection: case report and review of the literature. J Pediatr Gastroenterol Nutr 1999; 28 (1): 108-11
90. Aoyama T, Sunakawa K, Iwata S, et al. Efficacy of short-term treatment of pertussis with clarithromycin and azithromycin. J Pediatr 1996; 129: 761-4
91. Bace A, Zrnic T, Begovac J, et al. Short term treatment of pertussis with azithromycin in infants and young children. Eur J Clin Infect Dis 1999; 18: 296-8
92. Eskanazi B, Bracken B. Bendectin as a risk factor for pyloric stenosis. Am J Obstet Gynecol 1982; 144: 919-24
93. Mitchell AA, Schwingl PJ, Rosenberg L, et al. Birth defects in relation to Bendectin use in pregnancy. Am J Obstet Gynecol 1983; 147: 737-42

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