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Title: No association between macrolide treatment in infancy and later pyloric stenosis in Sweden

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ETHICAL APPROVAL
The study was approved by the Regional Ethical Review board in Stockholm, Sweden (DNR 2011/2012-31/5 and 2012/1179-32).

COMPETING INTERESTS
All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. JFL, CL, AKÖ, and CA claim no conflict of interest related to the submitted work.

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Dear EJE,

In a recent paper in the BMJ, Lund *et al* reported an increased risk of infantile hypertrophic pyloric stenosis (IHPS) in infants exposed to macrolides, especially during days 0-13 (adjusted rate ratio (ARR)=29.8, 95%CI=16.4-54.1)[1]. The excess risk decreased rapidly with exposure later in life (days 14-120: ARR=3.24; 95%CI=1.20-8.74). Also a retrospective cohort study of children to US uniformed personnel recorded in the TRICARE database found a positive association between macrolides and IHPS[2]. In Sweden, one of the most common uses of erythromycin in newborns is to stimulate the gastrointestinal motility and we believe that the positive association between macrolides and IHPS is due to reverse causation [3]. Lund *et al* also mention that some macrolides are used for dysmotility in smaller children.

In a nationwide cohort of 582,494 children born between July 2005 and December 2010 in Sweden we examined the use of macrolides and the risk of IHPS.

METHODS

Data on pregnancy and birth factors were obtained from the Swedish Medical Birth Registry[4], while we used the Swedish Patient Registry[5] (contains data on hospital-based outpatient and inpatient care since 2001) to identify cases of IHPS (international classification of disease (ICD) codes; Q40.0, K31.1). We defined exposure as macrolide use (ATC code: J01FA) according to the Swedish Prescribed Drug Registry[6]. In Sweden, the Prescribed Drug Registry contains dispensed drug data but not data on over the counter drugs or drugs administered at hospital. A priori we had planned to use Cox regression to examine the risk of IHPS in children exposed to macrolides.

RESULTS

Four hundred and fifty (450) children had a diagnosis of IHPS (equivalent to 0.8 per 1000 births). The median age at diagnosis was 35 days, ranging from birth to 1038 days (four children had their first recorded diagnosis of IHPS beyond the age of 500 days).

Some 17,659 children had a record of macrolides, but only 32 had been prescribed macrolides (all had received erythromycin) during days 0-13 (the youngest was 5 days old) and 1275 children during days 14-120. In total 240 children had a record of macrolides by day 35 (238 (99%) with erythromycin). No infant in our study had a record of macrolides prior to IHPS, but 18 children had received macrolides after the IHPS diagnosis. No case among 240 exposed corresponds to a proportion of 0% with a 95% confidence interval of 0-1.5% based on the binomial distribution.

DISCUSSION

Assuming a risk ratio of 30 for the association between macrolides during day 0-13 and IHPS, there would be a probability of 47% to find no cases among 32 exposed, based on the IHPS incidence in Sweden. Thus our data do not contradict the findings of Lund *et al*, and we cannot rule out that early macrolide exposure contributes to IHPS, especially when administered in high doses. Besides, a major weakness of our study is that we did not have access to antibiotics administered in hospital. For newborns, hospital-administered antibiotics are an important exposure. Still, we were able to identify 240 children with macrolides in the first 35 days of life and none developed IHPS. The lack of IHPS cases among individuals exposed to macrolides meant that we were unable to adjust our data for sex, firstborn status, and prematurity.

While the lack of individuals with IHPS and prior macrolides does not allow us to calculate any risk estimate for the association with IHPS it strengthens our belief that macrolides is a rare cause of IHPS. None of the 240 children had a record of IHPS. Assuming the risk ratios estimated by Lund *et al* are true, the population attributable fraction based on Swedish macrolide prescription frequencies would be 0.6%, corresponding to approximately one case every 4^{th} year.

In conclusion, the current study found no association between macrolide exposure and later IHPS, but our results were based on small numbers of exposed individuals.

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