Available online at www.sciencedirect.com
SCIENCE DIRECT
Reproductive Toxicology 20 (2005) 209–214
Reproductive Toxicology
www.elsevier.com/locate/reprotox

Is erythromycin therapy teratogenic in humans?

Bengt A.J. Källén [a,*], Petra Otterblad Olausson [b], Bengt R. Danielsson [c]

[a] *Tornblad Institute, Lund University, Biskospgatan 7, SE-22362 Lund, Sweden*
[b] *Centre for Epidemiology, National Board of Health and Welfare, Stockholm, Sweden*
[c] *Department of Toxicology, Uppsala University, Uppsala, Sweden*

Received 3 December 2004; received in revised form 10 January 2005; accepted 28 January 2005
Available online 2 March 2005

Abstract

The possible teratogenic effect of erythromycin therapy, noted previously, was studied. Women who had taken erythromycin or penicillin V in early pregnancy and their infants were studied, using the Swedish Medical Birth Register where information on drug use during pregnancy was recorded based on interviews in early pregnancy. The risk for any congenital malformation after erythromycin therapy (but not after penicillin V therapy) was increased (odds ratio 1.24, 95% confidence interval: 1.01–1.51) and this was due to an effect on cardiovascular malformations (odds ratio 1.92, 95% CI: 1.37–2.68). There was also an indicated increased risk for pyloric stenosis (risk ratio 3.0, 95% CI: 1.1–8.5 after exposure in early pregnancy). Various explanations to the finding are discussed, one of them linked to the fact that erythromycin inhibits a specific cardiac potassium channel (IKr) which seems to play a major role in cardiac rhythm regulation in the early embryo. Potent blocking drugs cause as a class effect cardiac defects in animal experiments.

Keywords: Erythromycin; Teratogenicity; Cardiovascular defects; Pyloric stenosis; Epidemiology; IKr; hERG

1. Introduction

There is incomplete information in the literature regarding a possible teratogenic effect of erythromycin therapy. In the Collaborative Perinatal Project [1] during the 1950s and early 1960s, only few such exposures were recorded. Among 79 children exposed prenatally, eight were malformed yielding a relative risk of less than 1.5. No significant teratogenic effect was reported from the Hungarian case–control surveillance of congenital anomalies [2], but an increased risk was found for cardiovascular defects for erythromycin use during any part of the pregnancy (odds ratio = 1.6, 95% CI: 1.1–2.4, Table 3 in that paper). The same odds ratio was seen for exposures during the second–third months of pregnancy, but only eight cases occurred, and the increased risk was not statistically significant. Among women who had an infant with a cardiac defect, an over-risk for erythromycin use in early pregnancy has been described with an odds ratio of 1.91 (95% CI: 1.30–2.80) [3]. The present study extends that material with data for one further year and also makes a comparison with penicillin V use.

Early (days 3–13) postnatal exposure of newborns to erythromycin therapy has been associated with an increased risk for pyloric stenosis [4] and it has also been suggested that maternal use of erythromycin during breastfeeding can be a risk factor for pyloric stenosis [5]. No association between prenatal use of erythromycin and pyloric stenosis was seen but an indicated such risk for other macrolides [6].

The present study gives a detailed description of delivery outcome after maternal erythromycin therapy in early pregnancy, based on the Swedish Medical Birth Register. Comparisons are made with all deliveries. A similar analysis is also made for maternal use of penicillin V.

2. Material and methods

The Swedish Medical Birth Registry [7] contains medical information on pregnancy, delivery, and the newborn in-

* Corresponding author. Tel.: +46 46 222 7536; fax: +46 46 222 4226.
E-mail address: embryol@embryol.lu.se (B.A.J. Källén).

0890-6238/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.reprotox.2005.01.010

fant for nearly all infants born in Sweden (a few percent are missing). The registry is formed from copies of the medical documents, identical in the whole country.

Data on drug use during pregnancy were included in the registry beginning in 1994. This information was obtained from midwife interviews at the first visit of the pregnant woman to the antenatal care centers, usually in weeks 10–12 and for more than 90% before the end of the first trimester. The information will thus mainly refer to first trimester use of the drugs. The registry also contains information on drugs prescribed by the antenatal care services during the pregnancy. All drug information is thus collected prospectively in relation to delivery.

From the registry, infants whose mothers had reported the use of erythromycin were selected when born between 1 July 1995 and the end of 2002. During this period, 677,028 infants (666,046 deliveries) were recorded in the register. Among them, 1844 (1813 deliveries) had been exposed to erythromycin before and 1831 (1806 deliveries) after the first antenatal care visit.

The comparison with maternal use of penicillin V was based on 9110 infants (8980 deliveries) exposed before the first antenatal care visit.

The following variables were studied:

Year of birth of the infant (1995–2002);
Maternal age divided into 5-year groups (−19, 20–24, etc.);
Parity (1, 2, 3, 4+);
Smoking in early pregnancy (unknown, none, <10 cigarettes per day, 10+ cigarettes per day);
Earlier miscarriage (none, 1, 2, 3+);
Use of other drugs;
Presence of congenital malformation.

Malformations were identified from three sources: the Medical Birth Register, the Swedish Register of Congenital Malformations, and the Hospital Discharge Register [8]. Duplicates were removed using the personal identification numbers of mother and infant and such numbers also enabled linkage between the Medical Birth Register and the other two registers. Personal identification numbers are given to every person living in Sweden and are widely used in society including in all health care. The Medical Birth Register and the Register of Congenital Malformations identify malformations in the neonatal period while the Hospital Discharge Register identify malformations recorded among the discharge diagnoses at any hospitalization up to the end of 2002.

Statistical analysis was made using Mantel–Haenszel's procedure and risks were estimated as odds ratios (OR) and 95% confidence intervals (95% CI) using Miettinen's test-based method. When expected numbers were low, risk ratios as observed/expected numbers were calculated instead and 95% CI were determined from Poisson models.

3. Results

3.1. Maternal and infant characteristics at erythromycin or penicillin V therapy in early pregnancy

Table 1 compares maternal characteristics in relation to the use of the two drugs. It can be noted that young maternal age is associated with use of erythromycin but not with penicillin V. For both drugs, less use is seen at parity 1 than at higher parity. Both drugs are associated with an increased smoking rate of the same magnitude, even though it is not statistically significant for erythromycin therapy. Previous miscarriage is associated with both drugs even though the odds ratios are relatively small. No excess of preterm delivery, low birth weight, or small for gestational age among singleton infants is seen for any of the drugs.

3.2. Use of other drugs

Among women reporting the use of erythromycin, 305 (17%) also reported the use of some other antibiotic. The majority, 202, had used penicillins, 33 tetracyclines (23 of them doxycycline), 39 cephalosporines (23 of them cefadroxil), 29 clindamycin, and 14 metronidazole.

An analysis of concomitant use of other drugs (Table 2) showed statistically significant associations between erythromycin and some specific groups of drugs, including drugs used for stomach ulcer, glucocorticoids, opiates (nearly exclusively dextropropoxyphene), mild analgesics, anti-asthmatic drugs, and cough medicines. A similar pattern was seen also after penicillin V but then some further significant associations appeared: hormonal contraceptives, NSAID, and antihistamines. For NSAID and mild analgesics, the association was significantly stronger with penicillin V than with erythromycin while the opposite was true for glucocorticoids, anti-asthmatic drugs, and cough medicines.

3.3. Congenital malformations

Among the 1844 infants exposed to erythromycin in early pregnancy, 103 were identified as having a congenital malformation (5.6%). The corresponding numbers for infants exposed to penicillin V was 420 with malformations among 9110 exposed infants (4.7%). The rate of congenital malformations among all infants born was 4.6%. The odds ratio for having a congenital malformation after exposure to erythromycin, adjusted for year of birth, maternal age, parity, and smoking was 1.24 (95% CI: 1.01–1.51) and after exposure to penicillin V it was 1.02 (95% CI: 0.92–1.13).

Tables 3 and 4 list the congenital malformations recorded among the infants that had been exposed for erythromycin in early pregnancy. Among them, 34 infants (1.8%) had a cardiovascular malformation diagnosis (excluding infants with chromosome anomalies and also infants with patent ductus arteriosus or single umbilical artery), which is a high rate. Among infants exposed to penicillin V, 86 (0.9%) had such