DRUG INFORMATION
Jonathan Banks
Bob Buckham
Sharon Gardiner

Canterbury DHB
District Health Board
Te Poari Hauora o Waitaha

CLINICAL PHARMACOLOGY
Murray Barclay
Evan Begg
Chris Hutchinson
Petra Lowe
Jane Vella-Brincat
Mei Zhang

SAFETY OF TRIMETHOPRIM IN PREGNANCY

Question:
What are the risks associated with the inadvertent use of trimethoprim in the first few weeks of pregnancy?

Answer:
Background
As a general rule, it is preferable to avoid all drugs in pregnancy, unless the potential benefits are perceived to outweigh any risks. The risk of foetal malformation is greatest during organogenesis (18 to 55 days post conception)[1,2]. The foetus is reported to have relative resistance to the toxic effects of drugs in the initial few weeks of pregnancy (from conception until about day 17), prior to implantation[2].

Trimethoprim's half-life is about 10 hours (range: 9-17) indicating that the majority will be eliminated from the maternal circulation within two days (five half-lives) of completing a course.

Trimethoprim and pregnancy
Trimethoprim is a folate antagonist and has the potential to disrupt many metabolic pathways including nucleic acid synthesis. Therefore, trimethoprim is usually avoided during pregnancy especially during the first trimester[1,3,4].

Briggs *et al.,*[1] reported that an increase in foetal malformations has not been observed in *"several hundred"* pregnancies described in published case reports and trials. However, they also described a surveillance study where 2,296 newborns had first-trimester exposure to trimethoprim (+ sulphamethoxazole). They reported 126 major birth defects (98 expected) including (observed/expected) 37/23 cardiovascular defects, 3/4 oral clefts, 1/1 spina bifida, 7/7 polydactyly, 3/4 limb reduction defects and 7/5 hypospadias. Only the cardiovascular defects are suggestive of an association with trimethoprim[1].

Hernandez-Diaz *et al.,*[5] used information from a multicentre surveillance program to determine whether folic acid antagonists increased the risk of cardiovascular or urinary tract defects, or oral clefts. Folic acid antagonists consisted of dihydrofolate reductase inhibitors (DRIs e.g. trimethoprim, methotrexate, sulphasalazine and agents that alter folate's disposition by some other means such as increasing degradation e.g. carbamazepine, phenytoin. Only the DRIs will be discussed here.
Case subjects were infants who were born with cardiovascular defects (n=3,870), oral cleft (n=1,962) or urinary tract defects (n=1100). Infants with co-existing neural-tube defects were not included. Control subjects were infants with malformation other than those included in the case group, or neural tube or limb-reduction defects.
Mothers were questioned retrospectively within 6 months of delivery regarding drug use during pregnancy. The DRIs were associated with increased risk of cardiovascular defects (relative risk (RR): 3.4; 95% confidence interval (CI): 1.8-6.4) and oral cleft (RR: 2.6; 95% CI: 1.1-6.1). These risks were increased when exposure occurred in the second and third months after the last menstrual period but not before or after this period. Too few urinary tract defects were available to be included in analysis.

The number of pregnancies with exposure to trimethoprim in the second or third month after the last menstrual period was very small. Relative risks were only able to be calculated for cardiovascular defects (4.2; 95% CI 1.5-11.5)[5].
The risk of cardiovascular defects was reduced when folic acid-containing multivitamins were administered (insufficient data for assessment of effect of folic acid supplementation on oral cleft).

In a similarly designed study by the same authors, exposure to folic acid antagonists (includes DRIs such as trimethoprim and enzyme inducing anticonvulsants) during the two months after the last menstrual period (the period of neural tube development) was associated with a small increase in the risk of neural tube defects. The odds ratio for women exposed to folic acid antagonists compared with those not exposed was 2.8 (95% CI: 1.7-4.6). Specific odds ratio for trimethoprim was 4.8 (95% CI: 1.5-16.1). Folic acid supplementation protected against neural tube defects[6].

Conclusions:

Trimethoprim is usually avoided in pregnancy because of concerns regarding the effects of folate antagonism on rapidly dividing cells. However, the conceptus is thought to be relatively resistant to drug exposure in the first 1-2 weeks of pregnancy. The half-life of trimethoprim is relatively short, such that the majority will be eliminated within two days of completing the course. First-trimester administration beyond this time may be associated with an increased risk of neural tube, cardiovascular and urinary tract defects, and oral clefts. These are relatively rare events and the majority of exposures will not result in an abnormal foetal outcome. These risks also appear to be reduced when folic acid containing supplements have been administered.

References:

1. Briggs GG *et al.* Drugs in Pregnancy and Lactation (5th ed), 1998
2. Drugdex, Micromedex database
3. Ferner RE Adverse Drug Reaction Bulletin 1993; 161: 607-10
4. Hernandez-Diaz S *et al.* N Engl J Med 2000; 343: 1608-14
5. Hernandez-Diaz S, Mitchell AA. N Engl J Med 2001; 344(12): 934-5
6. Hernandez-Diaz S *et al.* Am J Epidemiol 2001; 153(1): 961-8

Date prepared:

October 2001