RISK OF FETAL EXPOSURE TO FOLIC ACID ANTAGONISTS

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*This Study is based in part on non-identifiable data provided by the Saskatchewan Department of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Department of Health.

Abstract
Background: Several folic acid antagonists are considered by the Food and Drug Administration (FDA) to be toxic or potentially toxic to fetuses, including some folic acid antagonists that were once considered safe, such as trimethoprim. Information on fetal exposure to folic acid antagonists is sparse.

Methods: In this study, we conducted a thorough search of English literature on human uses of various folic acid antagonists, and made an indirect estimation of potential exposure to folic acid antagonists during pregnancy by analyzing the data from the outpatient prescription drug database of the Canadian province of Saskatchewan.

Results: The numbers of women of reproductive age (16 to 44 years) with at least 1 prescription of dihydrofolate reductase inhibitors was 14 195 in 1977, 20 455 in 1991, and 16 054 in 1999. Corresponding figures for other folic acid antagonists were 2136, 1954, and 2720, respectively. According to these figures, the rates of prescription given to women of reproductive age in any particular calendar year were 8.45% (95% confidence interval [CI], 8.33%–8.57%) for dihydrofolate reductase inhibitors and 1.14% (95% CI, 0.67%–1.61%) for other folic acid antagonists.

Conclusions: Prescription of folic acid antagonists to women of reproductive age is quite frequent, and there has been no apparent decline in prescriptions in recent years. Increase in unplanned pregnancies in industrial countries, lack of adequate scientific evidence on the adverse effects of folic acid antagonists, potential ignorance in clinical practice, and conflicting needs to treat maternal diseases and to protect fetuses, can all lead to frequent prescription of potentially toxic folic acid antagonists to pregnant women, thus posing serious threat to the fetuses. In this paper, strategies that may be used to reduce the risk of fetal exposure to folic acid antagonists are proposed.

Résumé
Contexte : Plusieurs antagonistes de l’acide folique sont considérés par la Food and Drug Administration (FDA) comme étant toxiques ou potentiellement toxiques pour les fœtus, y compris certains antagonistes de l’acide folique ayant déjà été considérés comme étant sûrs, tels que le triméthoprime. Les données sur l’exposition fœtale aux antagonistes de l’acide folique sont peu abondantes.

Méthodes : Dans le cadre de cette étude, nous avons procédé à une analyse exhaustive de la littérature anglophone sur les utilisations chez l’homme de divers antagonistes de l’acide folique; de plus, nous avons effectué une estimation indirecte de l’exposition potentielle à ces derniers au cours de la grossesse, en analysant les données de la base de données sur les médicaments d’ordonnance pour patient non hospitalisé de la province canadienne de Saskatchewan.

Résultats : Le nombre de femmes en âge de procréer (de 16 à 44 ans) comptant au moins une prescription d’inhibiteurs de la dihydrofolate réductase était de 14 195 en 1977, de 20 455 en 1991 et de 16 054 en 1999. Les données correspondantes pour les autres antagonistes de l’acide folique étaient 2 136, 1 954 et 2 720, respectivement. Selon ces données (peu importe l’année civile examinée), les taux de prescriptions offertes aux femmes en âge de procréer étaient de 8,45 % (intervalle de confiance [IC] de 95 %, 8,33 %–8,57 %) pour les inhibiteurs de la dihydrofolate réductase et de 1,14 % (IC de 95 %, 0,67 %–1,61 %) pour les autres antagonistes de l’acide folique.

Conclusions : La prescription d’antagonistes de l’acide folique aux femmes en âge de procréer est assez fréquente ; aucun déclin apparent du nombre de prescriptions offertes ne semble être survenu au cours des récentes années. L’augmentation du nombre de grossesses non prévues au sein des pays industrialisés, l’absence de données scientifiques adéquates sur les effets indésirables des antagonistes de l’acide folique, la méconnaissance possible des faits en pratique clinique et la nature parfois conflictuelle de la nécessité de traiter les maladies maternelles tout en protégeant les fœtus sont tous des facteurs pouvant mener à l’offre fréquente de prescriptions d’antagonistes de l’acide folique potentiellement toxiques aux femmes enceintes, ce qui représente une grave menace pour les fœtus. Dans le cadre du présent document, des stratégies pouvant être utilisées pour réduire le risque d’exposition fœtale aux antagonistes de l’acide folique sont proposées.

Key Words
Folic acid antagonists; pregnancy; fetus; prescriptions, drug; abnormalities

Competing interests: None declared.

Received on August 22, 2003
Revised and accepted on November 13, 2003

INTRODUCTION

Folic acid antagonists comprise a broad spectrum of drugs with various therapeutic effects, including antimicrobial agents (e.g., trimethoprim, sulfasalazine), antikaliuretic agents (e.g., triamterene), cancer chemotherapy agents (e.g., methotrexate), antimalarial agents (e.g., pyrimethamine), anticonvulsant drugs (e.g., phenobarbital, phenytoin, primidone, valproic acid, and carbamazepine), and lipid-lowering drugs (e.g., cholestyramine). Folic acid antagonists can be divided into 2 groups: dihydrofolate reductase inhibitors, which displace folate from the enzyme and thereby block the conversion of folate to its more active metabolites; and other folic acid antagonists, which are primarily anticonvulsant drugs.

Several folic acid antagonists are considered by the Food and Drug Administration (FDA) to be toxic or potentially toxic to fetuses (Table 1), including those folic acid antagonists once considered safe, such as trimethoprim. The mechanisms of the 2 groups of folic acid antagonists may be different in their effects in inducing adverse fetal and infant outcomes. For example, antiepileptic drugs, such as phenytoin and phenobarbital, may have a direct toxic effect on the embryo.

This study reviews the available evidence on toxic effects of folic acid antagonists to fetuses, discusses reasons why fetuses might be exposed to potentially toxic folic acid antagonists, then estimates the frequency of potential fetal exposure to folic acid antagonists, and proposes strategies that may be used to reduce the risk of fetal exposure to folic acid antagonists.

METHODS

We conducted a thorough search of literature on human uses of folic acid antagonists. We searched the computerized database of MEDLINE using the key words folic acid antagonists, trimethoprim, sulfasalazine, triamterene, methotrexate, pyrimethamine, phenobarbital, phenytoin, primidone, valproic acid, carbamazepine, and cholestyramine. The search was restricted to English-language articles and human studies written from 1953 to 2003. This search strategy yielded 50,263 publications.

We first scanned the titles of these papers. We then read the abstracts of the papers that were relevant to our study purpose and read the full articles of those studies deemed significant. An additional reference search was also conducted. However, discretion by the authors has been used in deciding which of the papers would be included in the final analysis based on the clinical relevance and the quality of the study.

We also estimated potential exposure to folic acid antagonists during pregnancy. We used the data from the outpatient prescription drug database of the Canadian province of Saskatchewan. Because the linked mother/infant database in Saskatchewan was not available at the time of the analysis, we made an indirect estimation by calculating the rate for women of reproductive age (16 to 44 years) with at least 1 prescription for a dihydrofolate reductase inhibitor or other folic acid antagonist in a particular calendar year. To assess the temporal trends in the prescriptions, we analyzed three years’ data (1977, 1991, and 1999) from the Saskatchewan outpatient prescription drug database.

RESULTS

POTENTIAL TOXIC EFFECTS OF FOLIC ACID ANTAGONISTS TO FETUSES

In the embryonic period, the fetus goes through rapid growth,
morphogenesis, and differentiation. The neural tube begins to form as early as the third week post-fertilization. The neural crest cells, which eventually differentiate into the neural tube and the aorticopulmonary (or conal) septum, have their origin in the same area of the neural ectoderm where neural tube closure occurs. Undifferentiated cells from this area are interchangeable and can express either tissues. Folic acid, which is essential to the formation of nucleotides and amino acids, is vital to this process. Deficiency of folic acid (or folate) has been associated with numerous birth defects including most notably those of the neural tube and heart. A putative mechanism is that deficiency of folate during this period of rapid cell growth and division leads to either poor migration or poor differentiation of cells, resulting in developmental errors in early gestation that manifest ultimately in birth defects. Laboratory investigations have shown that folic acid depletion causes deoxyribonucleic acid (DNA) instability in human lymphocytes and increases apoptosis of human cytrophoblastic cells in vitro. Folic acid antagonists, by affecting folate metabolism and ultimately the synthesis of amino acids and nucleotides, may impair development by a similar mechanism.

Epidemiologic studies on the relationship of maternal exposure to folic acid antagonists and adverse pregnancy outcomes in offspring are sparse. Hernandez-Diaz et al. found that, compared with infants whose mothers had no exposure to folic acid antagonists, the relative risks of neural tube defects, cardiovascular defects, oral clefts, and urinary tract defects in infants whose mothers were exposed to folic acid antagonists varied from 2.2 to 6.9. They hypothesized that folic acid antagonists might cause birth defects, at least in part, by depleting folic acid.

POSSIBLE CAUSES OF FETAL EXPOSURE TO POTENTIALLY TOXIC FOLIC ACID ANTAGONISTS

The Food and Drug Administration (FDA) has created a classification system for the pregnancy risk of prescription drugs. According to this classification system, prescription drugs can be classified as A, B, C, D, or X. Category A indicates that controlled studies in women have failed to demonstrate a significant risk to the fetus, and the possibility of fetal harm appears remote. Vitamins are classified as Category A. Category B is assigned to drugs in which either animal reproduction studies have not demonstrated a fetal risk to the fetus, or animal-reproduction studies have shown an adverse effect that was not confirmed in well-controlled studies in women. Most of the minerals are classified as Category B. For a drug to be classified as Category C, either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal effects, or other), and there are no controlled studies in women, or studies in women and animals are not available. Category C drugs, such as selective serotonin reuptake inhibitors (SSRIs) and gentamicin, should be given only if potential benefits justify the potential risks to the fetus. Category D drugs have shown positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk. For example, Category D drugs may be needed in a life-threatening situation, or for a serious disease for which safer drugs cannot be used or are ineffective. Drugs in this category, such as phenytoin and antineoplastics, will have an appropriate statement in the "warnings" section of the labeling. Category X is used for those drugs in which studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience, or both, and the risk of using the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant. Category X drugs, such as misoprostol, have an appropriate statement in the "contraindications" section of the labeling.

However, despite prominent warnings of its potential adverse effects, the use of isotretinoin in pregnancy continues to be reported. There is a risk that FDA class C, D, and X drugs may be prescribed to and taken by pregnant women if they or their physicians are not aware of the pregnant status. In industrial countries, approximately half of all pregnancies are unplanned, suggesting a high probability of accidental exposure during pregnancy to drugs with fetal risk.

Valance has argued that drugs could cause fetal death or damage at any stage of pregnancy. Since drugs have the greatest potential to cause gross malformations during organogenesis in the first trimester (17 to 60 days), Valance has recommended that all drugs should be avoided during the first trimester. In contrast, Czeizel suggested that exaggeration over the teratogenicity of drugs may cause unnecessary anxiety in women of childbearing age and increases the likelihood of doctors practising defensive medicine. Thus, necessary drug treatment may sometimes not be prescribed, resulting in exacerbation of diseases such as epilepsy, depression, hypertension, and genitourinary infections.

ESTIMATION OF FETAL EXPOSURE TO FOLIC ACID ANTAGONISTS

The indirect estimation of potential exposure to folic acid antagonists during pregnancy, achieved through the analysis of the data from the Saskatchewan outpatient prescription drug database, suggested the numbers of women of reproductive age (16 to 44 years) with at least 1 prescription for a dihydrofolate reductase inhibitor were 14, 195, 20, 455, and 16, 054 in 1977, 1991, and 1999, respectively (Table 2). Corresponding numbers for other folic acid antagonists were 2136, 1954, and 2720, respectively, in these years (Table 2). Assuming that the rate of exposure to folic acid antagonists in pregnant women was halved, as compared to the rate of exposure in nonpregnant women of the same age, because of concerns over fetal risk and differences in demographic profile, the potential fetal exposure would be 4.80% for any folic acid antagonists, 4.23% for
Table 2. Number of Women Aged 16 to 44* with 1 or More Prescriptions of Folic Acid Antagonists in a Particular Calendar Year in Saskatchewan, Canada

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Dihydrofolate reductase inhibitors</td>
<td>14 195</td>
<td>20 455</td>
<td>16 054</td>
<td>16 901</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>11 851</td>
<td>17 934</td>
<td>14 513</td>
<td></td>
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<tr>
<td>Triamterene</td>
<td>2217</td>
<td>2516</td>
<td>1285</td>
<td></td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>372</td>
<td>241</td>
<td>162</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>8</td>
<td>155</td>
<td>321</td>
<td></td>
</tr>
<tr>
<td>Pyrimethamine</td>
<td>17</td>
<td>8</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2136</td>
<td>1954</td>
<td>2720</td>
<td>2270</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>1572</td>
<td>465</td>
<td>239</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>813</td>
<td>493</td>
<td>361</td>
<td></td>
</tr>
<tr>
<td>Primidone</td>
<td>152</td>
<td>52</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>262</td>
<td>815</td>
<td>888</td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>0</td>
<td>445</td>
<td>1376</td>
<td></td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>27</td>
<td>184</td>
<td>146</td>
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</table>

*The population figures for women aged 15 to 44, excluding registered Indians (for whom we do not have drug data because their prescriptions are covered federally), are 195 570, 207 116, and 202 376 for 1977, 1991, and 1999, respectively. Assuming equal distribution within the 15- to 19-year-old age group, we could subtract 9500, 6600, and 7000, respectively, from these figures, to exclude 15-year-olds from the covered population (for consistency with the folic acid antagonist figures), providing denominators of approximately 186 000, 200 500, and 195 300, for 1977, 1991, and 1999, respectively. Using these numbers as denominators in the rate-of-use calculations will give slightly different figures than those presented. The actual number of users of pyrimethamine in 1999 was suppressed due to a cell size less than 5 (i.e., there may have been 1 to 4 users, rather than 0 as presented in the table). A woman could be counted only once in the dihydrofolate reductase inhibitors group and only once in the "other" folic acid antagonists group. The sum of users of trimethoprim, triamterene, sulfasalazine, methotrexate, and pyrimethamine does not equal the total number of users of dihydrofolate reductase inhibitors because a woman could be counted once for each drug, but was only counted once in the dihydrofolate reductase inhibitors group, regardless of the number of drugs that she used. Likewise, the sum of users of phenobarbital, phenytoin, primidone, carbamazepine, valproic acid, and cholestyramine does not equal the total number of users for the "other" folic acid antagonists group.

dihydrofolate reductase inhibitors, and 0.57% for other folic acid antagonists. Based on the estimation of frequency of exposure to folic acid antagonists in the control subjects of a case-control study,6 the potential fetal exposure to any folic acid antagonists would be 0.8%; to dihydrofolate reductase inhibitors, 0.2%; and to other folic acid antagonists, 0.6%. Our population-based study suggested that the potential fetal exposure to dihydrofolate reductase inhibitors and other folic acid antagonists was much higher.

DISCUSSION

The frequent prescription of folic acid antagonists, including those with apparent fetal toxic effects, to women of reproductive age poses a serious threat of fetal exposure to potentially toxic drugs. Increased awareness through education is required to inform physicians, allied health personnel, and women of the risks of unplanned pregnancy in relation to toxic drugs. Further, large-scale epidemiologic studies are needed to assess the potential adverse effects of folic acid antagonists in pregnancy on a broad spectrum of fetal and infant outcomes, including major birth defects, severe fetal growth restriction, and neonatal morbidity. A large-scale study, using the Saskatchewan linked maternal/infant database, is planned.

Physicians caring for women of reproductive age who have medical conditions for which folic acid antagonists are often prescribed may need to consider changing to alternative pharmacologic treatments. For example, urinary tract infections that are often treated with trimethoprim could be more safely treated with alternative antibiotics without decreasing the cure rate of urinary tract infection. Further, women requiring treatment by folic acid antagonists should be fully informed about the potential effect of these drugs on a fetus or neonate. Women who must remain on folic acid antagonists during pregnancy could be given increased folic acid supplementation (4 mg po OD) until 8 weeks postconception. Other measures, such as obtaining information on the woman's last menstrual period at each visit, stronger communication about the importance of folic acid prophylaxis, consideration of a "consent form" for the use of folic acid antagonists during pregnancy, and the suggestion of alternatives in treating diagnoses that usually require folic acid antagonists, may also help to reduce fetal exposure to potentially toxic folic acid antagonists.

CONCLUSIONS

Prescription of folic acid antagonists to women of reproductive age is quite frequent, and there has been no apparent decline in prescriptions in recent years. Increase in unplanned pregnancies in industrial countries, lack of adequate scientific evidence on the adverse effects of folic acid antagonists, potential ignorance in clinical practice, and the need to treat maternal diseases can all lead to prescription of potentially toxic folic acid antagonists to pregnant women, thus posing serious threat to the fetuses. We propose that measures such as using alternative pharmacologic treatments, increasing folic acid supplementation
(to 4 mg po OD) until 8 weeks postconception, obtaining information on the woman’s last menstrual period at each visit, strengthening communication about the importance of folic acid prophylaxis, and using a “consent form” with women who take folic acid antagonists during pregnancy may help to reduce the risk of fetal exposure to folic acid antagonists. Further, a large-scale epidemiologic study has been planned, using the Saskatchewan linked maternal/infant database, to assess the potential adverse effects of folic acid antagonists in pregnancy on a broad spectrum of fetal and infant outcomes, including major birth defects, severe fetal growth restriction, and neonatal morbidity.

ACKNOWLEDGEMENTS

The authors thank staff of Saskatchewan Health for providing data from the provincial health services database. This study is funded by grants from the Canadian Foundation for Innovation (grant # CFI/OIT3189) and from the Physicians’ Services Incorporated (Grant#PSI102-23). Dr. Wen is a New Investigator of the Canadian Institutes for Health Research (CIHR) and recipient of a CIHR/R & D research allowance, and Dr. Walker is a Career Scientist of the Ontario Ministry of Health and Long-Term Care.

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