

CaseMed-Pregnancy Resource Newsletter

November 2007

MEDICAL STUDIES

Thalidomide AE reports defended by Brazil govt. Pharma Marketletter, 2007; October 8

The Brazilian Ministry of Health has defended its policy on the use of thalidomide for the treatment of erythema nodosum leprosum. The UK's Financial Times reports that three children have been born with severe physical disabilities after the drug's use by women in early pregnancy. The adverse events are a throwback to the drug's problems in the 1960s, which led to its withdrawal worldwide as a sedative. Thalidomide is approved in the USA for the acute treatment of cutaneous manifestations of moderate-to-severe ENL, as well as a maintenance therapy for the prevention and suppression of the disease's recurrence. In Brazil, the three cases are believed to involve the use of the drug as a sedative in two cases and for a pregnant woman with ENL in the third. The World Health Organization and the Pan-American Health Organization have offered free replacements for thalidomide in recent years, after 33 confirmed similar cases in Brazil from 1965 to 1994.

Extent of medication use in breastfeeding women

*Stultz EE, Stokes JL, Shaffer ML, et al
Breastfeed Med, 2007; 2(3): 145-51*

The types and extent to which medications are used by breastfeeding women have not been thoroughly investigated in the United States. The aim of this study was to explore the relationship between medication use during pregnancy and lactation. A survey was given to a cohort of women who delivered their babies at a single centre. Participants were asked to record the medications they had taken during pregnancy and were contacted each month during lactation to determine what medications they had taken. Results showed that the participants took more prescription and nonprescription medications breastfeeding than they did during pregnancy. Many of the medications taken have unknown safety for the breastfed infant. The authors conclude that further research should be directed toward determining the safety of medications commonly used during lactation and to promoting the labeling of these medications.

A randomized comparison between intravaginal misoprostol and prostaglandin E2 for labor induction

*Sifakis S, Angelakis E, Avgoustinakis E, et al
Arch Gynecol Obstet, 2007; 275(4): 263-7*

The aim of this randomized study was to compare the effectiveness, safety, and side effects of 6 h vaginal misoprostol versus vaginal prostaglandin E(2) (PGE(2)) for labor induction. In the misoprostol group, oxytocin was used less frequently, but there was a higher prevalence of tachysystole. No statistically significant differences were observed between the two groups in regards to abnormal patterns of fetal heart rate, the mode of delivery, or the need for neonatal intervention. In conclusion, the intravaginal administration of 50 mug misoprostol at 6 h interval

(maximum three doses) is comparable in safety, but more effective for induction of labor than 3 mg intravaginal PGE(2).

Thiopurine treatment in inflammatory bowel disease: clinical pharmacology and implication of pharmacogenetically guided dosing

***Teml Alexander, Schaeffeler Elke, Herrlinger Klaus R., et al
Clin Pharmacokinet, 2007; 46(3): 187–208***

This review summarizes the clinical pharmacological aspects of thiopurines in the treatment of chronic inflammatory bowel disease (IBD). Current knowledge of pharmacogenetically guided dosing is discussed for individualization of thiopurine therapy, particularly to avoid severe adverse effects. Several studies indicate that thiopurine therapy in IBD during pregnancy is safe, thus, azathioprine/mercaptopurine should not be withdrawn in strictly indicated cases of pregnant IBD patients. However, breastfeeding is contraindicated during azathioprine /mercaptopurine therapy.

Brain morphology alterations in the basal ganglia and the hypothalamus following prenatal exposure to antiepileptic drugs

***Ikonomidou C, Scheer I, Wilhelm T, et al
Eur J Paediatr Neurol, 2007; 11(5): 297–301***

Driven by results of experimental work showing that AEDs may induce neuronal death in the developing rodent brain, the authors wanted to explore whether prenatal exposure to AEDs (PAE) may result in structural changes in the human brain. For this purpose they investigated a group of healthy young adults with PAE and a group of age matched unexposed healthy controls by magnetic resonance imaging of the brain. Ikonomidou and colleagues conclude that PAE causes subtle morphological changes in grey matter of the human brain which conform with lower cell numbers in the basal ganglia and the hypothalamus.

What is the chance of a normal pregnancy in a woman whose fetus has been exposed to isotretinoin?

***Sladden Michael J, Harman Karen E
Arch Dermatol, 2007; 143(9): 1187–8***

No abstract is available.

Taking ACE inhibitors during early pregnancy: is it safe?

***Ray Joel G, Vermeulen Marian J, Koren Gideon
Can Fam Physician, 2007; 53(9): 1439–40***

This article begins with the following question: *I knew that angiotensin-converting enzyme (ACE) inhibitors were risky to use during late pregnancy because they can cause renal shutdown in the fetus. Recently I heard of a study that claimed first-trimester exposure (when many patients still are unaware of their pregnancies) can also cause major malformations. Is this proven?* The authors discuss the study by Cooper and colleagues that assess the association between exposure to ACE inhibitors during the first trimester of pregnancy and risk of congenital malformations. They conclude that while the study did suggest an increased risk of malformations after first-trimester exposure to ACE inhibitors among women treated for hypertension, they believe the study had serious limitations and preclude drawing any conclusions at present.

Treatment of acromegaly with pegvisomant during pregnancy: maternal and fetal effects

Brian Susan Riddle, Bidlingmaier Martin, Wajnrajch Michael P, et al
J Clin Endocrinol Metab, 2007; 92(9): 3374–7

The objective of this study was to describe the first case of successful use of pegvisomant during pregnancy in a woman with acromegaly. The case of a 26-yr-old female with acromegaly who had failed surgical and subsequent medical therapy but whose disease was well controlled on pegvisomant is presented. The woman then conceived and was continued on pegvisomant throughout her pregnancy. Both maternal and cord blood samples at parturition were collected, and later her breast milk was analyzed. The researchers concluded that pegvisomant therapy during gestation was safe and effective in their patient. Transplacental passage of pegvisomant was either absent or minimal, with a concentration highly unlikely to convey any significant pharmacodynamic effects on the fetal GH and IGF-I system. In addition, there was no evidence of substantial secretion of pegvisomant into breast milk.

Fetal safety of letrozole and clomiphene citrate for ovulation induction
Forman R, Gill S, Koren G, et al
J Obstet Gynaecol Can, 2007; 29(8): 668–71

No abstract is available.

Corticosteroids in perinatal medicine: how to improve outcomes without affecting the developing brain?
Baud O, Sola A
Semin Fetal Neonatal Med, 2007; 12(4): 273–9

According to the authors, antenatal glucocorticoid therapy remains one of the most striking successes in the perinatal management of complicated pregnancies that result in premature birth. The anti-inflammatory and maturative properties of fluorocorticoids are such that all women at risk of preterm delivery before 34 weeks gestation should be treated. Betamethasone is preferred to dexamethasone and no more than two courses, 2 weeks apart, should be given until the evidence from further controlled trials on repeated doses becomes available. In particular, the early use of postnatal dexamethasone should be avoided in preterm infants because of the deleterious effects on neurological development, including not only cerebral palsy but also cognitive function and psychiatric-related behavior. Treatment with other steroids should be restricted to the context of randomized controlled trials.

Are psychotropic drugs used in pregnancy?
De Las Cuevas C, de la Rosa MA, Troyano JM, et al
Pharmacoepidemiol Drug Saf, 2007; 16(9): 1018-23

The purpose of this study was to assess the prevalence and characteristics of psychiatric drug use in pregnancy. A prospective observational study was performed on a total of 1332 consecutive women admitted for delivery, during a 3-month period, in the public obstetric services of Tenerife Island. Results showed that less than 4% of the women recognized having a psychiatric disorder, and only 2.5% were receiving psychiatric drug treatment at the moment they knew they were pregnant; of those, 68.7% introduced substantial modifications in their treatment at that moment, 47.9% did not report any change with respect to the period before pregnancy and 35.4% recognized that their mood was worse than previously. Although patients affected by a psychiatric disorder registered a higher rate of abdominal delivery, no differences in delivery or obstetric complications were found between women with and without psychiatric illness or in relation to psychiatric drug treatment. The authors conclude that compared to the literature, the

studied population shows a lower rate of psychiatric problems and pharmacological treatment. This may reflect underrecognition or undertreatment.

Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: maternal characteristics

Wikner BN, Stiller CO, Källén B, et al

Pharmacoepidemiol Drug Saf, 2007; 16(9): 988-94

Use of benzodiazepine (BZD) drugs or hypnotic benzodiazepine receptor agonists (HBRAs) during pregnancy may represent a hazard for the fetus. Using the Swedish Medical Birth Register, the researchers identified 2149 pregnant women using BZDs or HBRAs. These women were compared with other women (n = 859 455) giving births during the same period. The following maternal characteristics were studied: age, parity, smoking habits, education, previous miscarriages, years of involuntary childlessness as an estimate of subfertility, concomitant drug use and some pregnancy complications. Results indicate that women using BZDs or HBRAs differ in many aspects from women not using those drugs. These differences may act as confounders in the analysis of pregnancy outcome.

Disease activity in pregnant women with Crohn's disease and birth outcomes: a regional Danish cohort study

Nørgård B, Hundborg HH, Jacobsen BA, et al

Am J Gastroenterol, 2007; 102(9): 1947-54

Crohn's Disease is associated with an increased risk of adverse birth outcomes. However, existing studies have not assessed the impact of disease activity during pregnancy. In their study, Nørgård et al examined the impact of disease on birth outcomes: LBW, preterm birth, LBW at term and CAs. All births by Crohn's Disease women in North Jutland County, Denmark, from January 1, 1977 to December 31, 2005, were evaluated in a cohort study based on linkage between the Danish National Registry of Patients and the Medical Birth Registry. After identification of all births by CD women, review of medical records allowed collection of clinical details (including disease activity and drug therapy during pregnancy). The authors conclude that disease activity during pregnancy only increased the risk of preterm birth (especially in those with high disease activity) and further research is needed to assess the critical impact of disease activity in larger cohorts of Crohn's Disease women.

Oral hypoglycaemic agents for diabetes in pregnancy - an appraisal of the current evidence for oral anti-diabetic drug use in pregnancy

Ho FL, Liew CF, Cunanan EC, et al

Ann Acad Med Singapore, 2007; 36(8): 672-8

The use of oral hypoglycaemic drugs in pregnancy is not recommended due to reports of fetal anomalies and other adverse outcomes in animal studies and in some human cases. However, recent studies have suggested that some oral hypoglycaemic drugs may be used in pregnancy. In this review, the authors analyzed literature obtained from a PubMed search of peer-reviewed journals on oral hypoglycaemic drug use in pregnancy and examined the results critically. They conclude that recent evidence shows promising findings in the safety and efficacy of some oral hypoglycaemic agents in treating pregnant diabetics. However, larger clinical studies are required to ensure the safety and efficacy of these drugs in pregnancy.

Risk of congenital anomalies in pregnant users of statin drugs

Ofori B, Rey E, Bérard A.

Br J Clin Pharmacol, 200; 64(4): 496-509

Evidence from animal studies suggest that statin medications should not be taken during pregnancy. This study examines the association between the use of statins in early pregnancy and the incidence of congenital anomalies. Three study groups were assembled: women prescribed statins in the first trimester (group A), fibrate/nicotinic acid in the first trimester (group B) and statins between 1 year and 1 month before conception, but not during pregnancy (group C). Among live-born infants, the researchers selected infants with any congenital anomaly diagnosed in the first year of life as cases. Controls were defined as infants with no congenital anomalies. The rate of congenital anomalies in the respective groups was then calculated. Ofori and colleagues did not detect a pattern in fetal congenital anomalies or evidence of an increased risk in the live-born infants of women filling prescriptions for statins in the first trimester of pregnancy. However, conclusions remain uncertain in the absence of data from non-live births.

The use of olanzapine in pregnancy and congenital cardiac and musculoskeletal abnormalities
Yeshayahu Y

Am J Psychiatry, 2007; 164(11): 1759-60

No abstract available.

Trends in folic acid supplement intake among women of reproductive age - California, 2002-2006

Centers for Disease Control and Prevention (CDC)

MMWR Morb Mortal Wkly Rep, 2007; 56(42): 1106-9

Daily intake of 400 microg of folic acid before conception can reduce the risk for having an infant with a neural tube defect (NTD) such as spina bifida or anencephaly. Although other risk factors for NTDs exist, such as diabetes, obesity, and family history of NTDs, prevention measures have focused predominantly on promoting folic acid consumption. To analyze trends in folic acid-containing supplement intake among California women aged 18-44 years during 2002-2006, the California Department of Public Health conducted trend analyses of data from the California Women's Health Survey. This report summarizes the results of those analyses, which indicated that although the overall prevalence of intake of folic acid-containing supplements remained stable from 2002 (40%) to 2006 (41%) in California, use of such supplements decreased among Hispanic women and women with less education. The CDC concludes that the development of additional targeted and evidence-based public health interventions for increasing folic acid intake among these populations is needed.

LAY PRESS NEWS

Roche's CellCept raises birth defect risks: FDA

Dixon K

Reuters.com, 2007; October 29

The FDA said on Monday that the Roche Holding AG organ rejection drug, CellCept boosts the risk of pregnancy loss in the first trimester and also the risk of congenital malformations. In its warning, the FDA cited a review of postmarketing data from 1995 to 2007 that found among 77 women exposed to the drug, 25 had a spontaneous abortion and 14 had a deformed infant or fetus.

According to the agency, prehuman studies of the drug did find some signs of fetal defects. The FDA has added a new boxed warning to the drug's label stating the increased fetal risk of ear and facial deformities and problems in limbs, the heart and other organs.

Prenatal HIV prevention combo reduces resistance
Reuters Health E-Line, 2007; November 7

The addition of a single dose of a two-drug combination can prevent the development of resistance in pregnant HIV-infected women who receive a short-course regimen of nevirapine (Viramune) to prevent transmission of the virus to their infant. The study (which appears in *The Lancet*) indicates that adding a single dose of tenofovir (Viread) and emtricitabine (Emtriva) to nevirapine can prevent the development of resistance to nevirapine and NNRTIs. The combination of tenofovir and emtricitabine is also available in one pill (Truvada). According to the authors, the regimen may still require certain refinements. "Despite its effectiveness, this intervention might need modification to provide the optimum protective effect," lead author Dr. Benjamin H. Chi and colleagues state. "Nevertheless, it is an important adjunct to regimens that incorporate (the NNRTI) nevirapine and should be considered in settings where drug combinations to be taken over several days might be impractical for patients or for local health infrastructure."

Obstetricians urge pregnant women to get flu shots
Reuters Health E-Line, 2007; November 6

The American College of Obstetricians and Gynecologists (ACOG) is urging pregnant women to get vaccinated as soon as possible. In a written statement, ACOG notes that flu vaccination is an essential part of prenatal care that provides protection to both mom-to-be and her baby. Pregnant women are particularly vulnerable to serious illness associated with the flu, and treating the flu can be risky, according to ACOG. "The antiretroviral drugs commonly prescribed to combat the flu have not been tested for safety and efficacy in pregnancy and their effects on the fetus are unknown, Dr. Sarah J. Kilpatrick, chair of ACOG's Committee on Obstetric Practice, warns in a statement. "Pregnant women who are using these drugs should do so with caution. Your best bet is to avoid the flu altogether, and vaccination can help you do that," Kilpatrick said. Additionally, flu vaccination during pregnancy allows the woman and the fetus to develop flu-fighting antibodies, especially important because infants from 0 to 6 months cannot be vaccinated," she added. According to ACOG, women can get a flu shot throughout their pregnancy and while breast-feeding. Pregnant women should not use the flu spray, which is inhaled instead of injected. It is only FDA-approved for use in non-pregnant individuals between the ages of 2 and 49 years.

Return of thalidomide
Rix J
Daily Mail, 2007; October 23: p.54-55

The *Lancet* has just reported that thalidomide may help increase life expectancy in older people with the incurable blood cancer multiple myeloma. Thalidomide is already being used by at least 13,000 people in Europe, on a special 'named patient' basis. But Pharmion, the company that distributes the drug in Europe (and supported the research) has applied for a licence, which means regulation would be less stringent and the number of users would substantially rise. For those affected by the thalidomide disaster, the idea of a new licence for the drug is a dilemma. On the one hand, they have no desire to deny anyone a drug that might help them. On the other, they don't want to see the birth of another generation of thalidomide-impaired people. Their fears are not unfounded. In Brazil - where the drug is used to alleviate the side effects of leprosy treatment

- 33 babies affected by thalidomide were born between 1969 and 1995. There were precautions in place to prevent pregnant women taking the drug, but 'drugs leak into the general population,' says Dr Claus Newman of the Thalidomide Trust. 'If a medicine seems to work then it will be passed from person to person, especially in a huge and relatively under-educated population such as Brazil's, and the warnings may not go with it.' Dr Newman adds: 'Thalidomide is an unforgiving substance. It only requires one tablet to be taken in the most sensitive period [20-36 days after conception] to almost guarantee damage to the baby.' The Pharmion Risk Management Programme - aimed at preventing any unborn child coming into contact with thalidomide - requires women of childbearing age to use two forms of contraception and have a pregnancy test every four weeks while on treatment. As the drug has been found in semen, men must also use a condom during and for four weeks after treatment. Doctors prescribing thalidomide and pharmacies dispensing it, have to be registered with the drug company and patients are provided with material about the dangers of thalidomide - including an interview with a thalidomide survivor person - before they can sign that they understand the risks. 'If the scheme is rigidly and skillfully enforced, it should indeed minimize the risks,' says Dr Newman, 'but you can't legislate for human folly or ignorance.' The current licence application is for the treatment of multiple myeloma. Most MM patients are over 65 and the majority are men. Researchers are looking at thalidomide for a wide range of immune system diseases, cancers and AIDS-related disorders. Furthermore, Pharmion is not the only producer of the drug. Others are making it and selling it - sometimes via the internet - with no safety procedures in place.

Thalidomide film revives compensation fight

Paterson T

The Independent, 2007; November 8; p.1

Germany's pharmaceutical industry spent more than a year trying to ban the film, but last night a moving, controversial and widely acclaimed television drama about the tragedy suffered by thousands of children crippled by the drug thalidomide was finally broadcast to an audience of millions. The two-part drama - entitled A Single Pill and shown at prime time - amounts to a savage indictment of Grünenthal in Aachen which first manufactured thalidomide, which was known in Germany as Contergan, in 1957. Lawyers for Grünenthal spent 18 months trying to ban A Single Pill, arguing that it mixed fact with fiction and distorted the truth. But last year, judges at Germany's constitutional court dismissed all objections to the film and ruled that in the interests of free speech it should be shown. Michael Souvignier, the producer, said yesterday that the court's decision amounted to a triumph for freedom of expression. "I had always believed we would win in the end, but we had no idea that it would take so long," he said. The film is expected to strengthen the case of thousands of now middle-aged thalidomide victims who have been fighting for decades for substantial increases in the meagre payments they receive as compensation for the disabilities inflicted on them more than 40 years ago. An estimated 12,000 children worldwide were born without or with severely disfigured limbs as a result of their mothers taking Contergan during pregnancy. The drug was marketed as a sleeping pill without side-effects and was sold without prescription. Grünenthal advertised the drug as being as "harmless as a sugar cube".