acting against it. Hence, it should be evaluated further. The current approach, exploring genetic variability in TE individuals is important to clarify thalidomide teratogenesis, and could aid in strategies of pharmacogenetics to diminish its use in Brazil.

http://dx.doi.org/10.1016/j.reprotox.2016.03.033

Drug transporter protein-mediated drug interactions during pregnancy and offspring outcome; with special emphasis on SSRIs and second generation antipsychotics

Heli Malm [1,2,*], Maria Ellfolk [1], Aleksi Tornio [2], Mikko Niemi [2]

[1] *Teratology Information, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*
[2] *Department of Clinical Pharmacology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland*

Background: Drug transporter proteins play an important role in the bioavailability and toxicity of drugs. P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) are the two important efflux transporter proteins in the human placenta. These proteins function as a blood-placental barrier by preventing drugs from entering the fetal circulation and protecting the fetus from exogenous chemicals. While concomitant use of transporter substrates may result in inhibition of function and increase fetal exposure to drugs, research in this field is only starting to emerge. It is not known if drug transporter protein-mediated drug interactions account for the previously reported inconsistent findings related to possible teratogenicity of second-generation antipsychotics and SSRIs, or if such interactions can also predispose to neonatal drug toxicity.

Objectives: To investigate if concomitant use of two or more drug transporter substrates during first trimester is associated with an increased risk of offspring major congenital malformations. Specifically, we will assess the risk of overall malformations in offspring of women using second-generation antipsychotics, and the risk of cardiac malformations in offspring of women using SSRIs or bupropion. We will also investigate if concomitant use of SSRIs together with a drug transporter substrate or inhibitor during the third trimester is associated with an increased risk of severe or prolonged neonatal adaptation problems.

Methods: This is a population-based cohort study based on the Drugs and Pregnancy project database in Finland. Data are derived from national health registers: the Medical Birth Register, the Register on Induced Abortions, the Malformation Register (all maintained by the National Institute for Health and Welfare), and the Prescription Register and Special Refund Entitlement Register both maintained by the Social Insurance Institution). Data in these registers have been collected during January 1st 1996–December 31st 2011 and include all births (live and still births), pregnancy terminations due to major congenital malformation, and information on drug purchases during pregnancy and 3 months before pregnancy. To this database we will further link data on individual drugs and their relation (substrate, inhibitor) to P-gp and BCRP from the University of Washington Metabolism and Transport Drug Interaction Database (DIDB). Offspring of women with concomitant use of two or more drug transporter substrates, or a combination of a substrate and an inhibitor, are compared to offspring of women using only one drug transporter specific substrate, and to unexposed.

Timelines: Linkage of the drug transporter substrate database data to the Drugs and Pregnancy database will start in May 2016. Final results with manuscript submission are expected in spring 2017.

http://dx.doi.org/10.1016/j.reprotox.2016.03.034

EMA warning for paternal use of mycophenolate: An unnecessary precaution?

Anneke L. Passier [1,*], Benedikte N. Cuppers [1], Eugène P. van Puijenbroek [1,2]

[1] *TIS, Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, The Netherlands*
[2] *University of Groningen, Department of Pharmacy, Pharmacotherapy and Pharmaceutical Care, Groningen, The Netherlands*

Introduction: In October 2015, the European Medicines Agency (EMA) has issued a warning that the transplant medicine mycophenolate (Cellcept®) must not be used in pregnancy unless there is no suitable alternative to prevent transplant rejection. Although the product information already contained warnings against use in pregnancy, these were now significantly strengthened, after a routine reassessment of the benefits and safety.

However, the suggested additional measures are not restricted to maternal use only. One of the recommendations states that sexually active (including vasectomized) men taking mycophenolate should use condoms during treatment and for 90 days thereafter, and their partner of childbearing potential should also use highly effective contraception in that period [1].

Background information: Maternal mycophenolate use during pregnancy is associated with an increase in congenital malformations including abnormal ear development, facial clefts, and heart defects [2]. A woman on mycophenolate is therefore advised to use effective contraception. If she wants to become pregnant, a preconceptional switch to azathioprine is usually considered. Paternal exposure to any medicine, including mycophenolate, has so far never been shown to result in an increased risk of congenital malformations. Two studies on over 250 pregnancies, fathered by men treated with mycophenolate showed pregnancy outcomes comparable with those of the general population [3]. There may be a possible effect on the motility of the sperm, but this would have a negative effect on the time to conception only. Another possible risk may be exposure of the fetus by the semen itself. However, limited studies show that transfer of medicines into sperm is very limited and unlikely to reach clinically relevant levels. The reason for the suggested paternal measures is not clear. It was explained to us as a precautionary measure, taken for several medicines with teratogenic properties.

Implications: The suggested paternal measures can have serious implications. A male user of mycophenolate who wants to start a family would not be able to become a father while he uses this medication. He would have to consider switching to another immunosuppressive like azathioprine, with the possible risk of acute rejection or serious side-effects. If he is not prepared to take that risk this may result in involuntary childlessness. Moreover, health care professionals are confronted with concerned (future) parents whose conception did take place under paternal use of mycophenolate.

Conclusion: In the absence of any indications for adverse pregnancy outcome after paternal exposure to mycophenolate, and considering the possible serious implications of the suggested measures, we do not support the strengthened precautionary EMA measures for male users of mycophenolate.

References

[1] http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/10/news_detail_002418.jsp&mid=WC0b01ac058004d5c1.
[2] M. Hoeltzenbein, E. Elefant, T. Vial, V. Finkel-Pekarsky, S. Stephens, M. Clementi, A. Allignol, C. Weber-Schoendorfer, C. Schaefer, Teratogenicity of mycophenolate confirmed in a prospective study of the European Network of Teratology Information Services, Am. J. Med. Genet. A 158A (March (3)) (2012) 588–596.
[3] A. Jones, M.J. Clary, E. McDermott, L.A. Coscia, S. Constantinescu, M.J. Moritz, et al., Outcomes of pregnancies fathered by solid-organ transplant recipients exposed to mycophenolic acid products, Prog. Transplant. 23 (June (2)) (2013) 153–157.

http://dx.doi.org/10.1016/j.reprotox.2016.03.035

Environmental contaminants in breast milk in Israel

Efreim Solomon[1,*], Elkana Kohn[2], Ronit Lubetzky[3,5], Dror Mandel[3,5], Josef Tovbin[4,5], Pam Factor-Litvak[6], Malka Britzi[1], Stefan Soback[1], Matitiahu Berkovitch[2,5]

[1] *Kimron Veterinary Institute, Residues Lab, Beit-Dagan, Israel*
[2] *Clinical Pharmacology and Toxicology Unit, Assaf Harofeh Medical Center, Zerifin, Israel*
[3] *Departments of Neonatology and Pediatrics, Dana Childrens' Hospital, Tel-Aviv Medical Center, Tel-Aviv, Israel*
[4] *Obstetrics and Gynecology Division, Assaf Harofeh Medical Center, Zerifin, Israel*
[5] *Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel*
[6] *Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA*

Brominated Flame Retardants (BFRs) are found in textiles, foam furniture, insulating foams, electrical equipment, kitchen appliances, televisions and computers. As BFRs are additive flame retardants, they are not chemically bound to products and have the potential to leach out of materials over time into the environment. Breast feeding is a major route of exposure in infancy. Taken together with the critical development of this age and the potential adverse effects of BFRs, it is important to monitor these contaminants in breastmilk. BFRs were measured before in Israel, but only as a pooled sample.

Our aim was to measure BFRs in breast milk. Colostrum samples from 50 women were collected during 2013–2015 from women at the maternity department. Samples were analyzed using GC–MS mass spectrometer. Various types of BFRs were analyzed: BDE-28, BDE-47, BDE-66, BDE-100, BDE-99, BDE-85, BDE-154 and BDE-153. The average concentrations (ng/g lipids) of the different congeners were: BDE-28: 2.2, BDE-47: 5.4, BDE-66: 1.7, BDE-100: 5.1, BDE-99: 6.1, BDE-85: 1.5, BDE-154: 1.9, BDE-153: 1.26. The sum of PBDEs concentration was 25.6 ng/g lipids. These results show that breastfed infants are exposed to significant BFRs amount. Assuming 750–1000 ml milk consumption per day, daily exposure is in the range of hundreds of micrograms. These values of BFRs in breast milk are above those found in some European countries, but less than in North America. Maternal exposure to BFRs and its significance for the nursing infant should be further investigated.

This study is supported by the Environment and Health Fund (EHF), Israel.

http://dx.doi.org/10.1016/j.reprotox.2016.03.036

Pregnancy outcomes in women who have taken leflunomide before or during pregnancy – A prospective case series from the German Embryotox center

Corinna Weber-Schoendorfer*, Evelin Beck, Christof Schaefer

Pharmakovigilanz- und Beratungszentrum Embryonaltoxikologie, Charité Universitätsmedizin, Berlin, Germany

Introduction: The teratogenic potential of leflunomide is still a matter of debate. Most case reports and two studies have not supported the notion of an increased risk of birth defects [1,2], but data are still limited. An excess of skeletal, heart and craniofacial defects was noted in animal studies at drug levels similar to therapeutic concentrations in humans. However, a teratogenic effect was questionable because maternal toxicity was observed as well. The manufacturer recommends stopping leflunomide 2 years before conception. Alternatively, wash-out therapy should be performed. Our primary objectives were to evaluate the occurrence of major malformations and fetal losses of exposed pregnancies recorded by the German Embryotox center.

Methods: Women with leflunomide therapy who or whose HCP spontaneously contacted Embryotox for risk assessment between 2000 and May 2015 were enrolled in our case series. Precondition was a leflunomide therapy in the time window of 2 years prior to conception till 10 weeks after conception and an uneventful pregnancy at first contact.

Results: Of 73 prospective maternal cases with initiated follow-up, 64 have been completed, 4 are pending and 5 were lost to follow-up. There were 45 post-conception and 19 pre-conception exposures. Of the latter the majority ($n = 17$) stopped their therapy within one year before conception with a median of 12 weeks prior to conception. For post-conception exposures the median duration of therapy during pregnancy was 6 weeks with 6 pregnancies starting leflunomide only after the last menstrual period (LMP), namely between week 1 and 6 + 1 day. Wash-out therapy with colestyramine and activated charcoal was reported in 33/64 pregnancies. Eighteen pregnancies were electively terminated, mostly because of fear of teratogenic risk, none because of fetal malformations. Ten pregnancies resulted in a spontaneous abortion. Among the 39 live-born children (including twins) there was one major malformation, an esophageal atresia with tracheoesophageal fistula after leflunomide exposure until gestational week 5 + 4 days and detoxification from week 8 till 10 + 1 day after LMP. The only concomitant medication was prednisolone. Of the 20 live-born children with 1st trimester exposure wash-out therapy was reported in 14 cases, however timing of colestyramine therapy was not clear in four of these cases.

Conclusion: In line with previously published studies our case series support the hypothesis that leflunomide is not a major human teratogen. Nevertheless, a detailed fetal ultrasound is recommended in cases of (unintended) exposure during pregnancy.

This work was supported by the German Federal Institute for Drugs and Medical Devices (BfArM).

References

[1] C.D. Chambers, D.L. Johnson, L.K. Robinson, S.R. Braddock, R. Xu, J. Lopez-Jimenez, et al., Birth outcomes in women who have taken leflunomide during pregnancy, Arthritis Rheum. 62 (May (5)) (2010) 1494–1503.
[2] M. Cassina, D.L. Johnson, L.K. Robinson, S.R. Braddock, R. Xu, J.L. Jimenez, et al., Pregnancy outcome in women exposed to leflunomide before or during pregnancy, Arthritis Rheum. 64 (July (7)) (2012) 2085–2094.

http://dx.doi.org/10.1016/j.reprotox.2016.03.037