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Trends in Paediatric Pharmacology and Toxicology

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Morales-Suarez-Varela MM, Bille C, Christensen K, Olsen J. Smoking habits, nicotine use, and congenital malformations. Obstet Gynecol 2006;107:51–57.

Many pregnant women smoke during the early phases of their pregnancies. Due to the potential fetotoxic effects of smoking, more pregnant women are recommended to quit smoking. To aid smoking cessation, some women participate in smoking cessation programs that may utilise nicotine substitute products. However, the fetotoxic effects of these therapies have yet to be defined. Recently, Danish researchers examined whether maternal **smoking and nicotine substitutes** were associated with **congenital malformations** during the first 12 weeks of pregnancy. In the Danish National Birth Cohort, 20,603 smoking mothers and 56,165 non-smoking mothers were indentified. An interview was used to obtain the smoking history and use of nicotine substitutes in the smoking and nonsmoking mothers. During the interview, the mothers were asked which weeks of gestation they were smoking, how much they smoked, type of tobacco they used, and if they used nicotine gum, patches or inhalers during the first 12 weeks of pregnancies. Results showed that smoking mothers were younger, weighed less, consumed more alcohol, and had a lower educational background when compared to non-smoking mothers. The infants born to mothers who only used nicotine substitutes, had a slightly relative increased in congenital malformations (relative prevelance ratio = 1.61 95%CI: 1.02 – 2.58). The researchers concluded that, although there was no increased overall prevalence of congenital malformation among smokers, there was an increased in malformation risk in nonsmokers using nictotine substitutes.

Clark RH et al. Emperic use of ampicillin and cefotaxime, compared with ampicillin and gentamicin, for neonates at risk for sepsis is associated with an increased risk of neonatal death. Pediatrics 2006;117:67–74.

In the neonatal intensive care unit, empirically treating a patient for potential sepsis is a common practice due to the increased mortality with delayed treatment. Common antibiotics used in sepsis evaluations include **ampicillin/ gentamicin or ampicillin/and a cephalosporin**. A recent study compared outcomes of in inborn neonates treated with either ampicillin/gentamicin or ampicillin/cefotaxime in the first three days of life. Cohorts were selected retrospectively from a deidentified administarative data set. There was a total of 24,111 patients selected for the cefotaxime group while 104,803 were selected for the gentamicin group. Extremely premature infants comprised approximately 1731 of the cefotaxime group compared to 5916 in the gentamicin group. The results were evaluated after an online survey was completed by participating Pediatrix physicians. Primary reasons a participating physician chose to use cefotaxime over gentamicin were potential ototoxic/nephrotoxic effects of gentamicin therapy, suspected perinatal asphyxia, or culture-suspected or proven Gram-negative meningitis. Interestingly, the results of logistic modelling showed increased mortality rates in the ampicillin/cefotaxime group when compared to the ampicillin/gentamicin group (OR 1.5; 95% CI: 1.4–1.7). Upon further analysis, the researchers found neonates who were treated with cefotaxime were slightly more immature and had lower birthweights. Factors found to be associated with death include: immature gestational ages, need for assisted ventilation, perinatal asphyxia, or a major anomaly. The authors conclude that the empiric use of ampicillin/ cefotaxime in the NICU is associated with increased risk of death. They suggest others examine their own practices and encourage studies to validate or dismiss their observations.

Manzoni P, Arisio R, Mostert M et al. Prophylactic fluconazole is effective in preventing fungal colonization and fungal systemic infections in preterm neonates: a single-center, 6-year, retrospective cohort study. Pediatrics 2006;117:e22–e32.

The advantages of **prophylactic fluconazole** for fungal infections have been well established in adult and paediatric patients with haematologic malignancies and immunodeficiencies. However, there is controversy regarding prophylactic antifungal use in **neonates**. Four hundred and sixty-five neonates were included in a recent 6 year retrospective, nonrandomised interventional study with historical controls. Those born between 1998 and 2000 served as the historical controls (no fluconazole prophylaxis = Group A). Those born between 2001 and 2003 were given fluconazole prophylaxis (Group B) through day of life 30 or 45 depending on their birth weight. Fluconazole prophylaxis decreased overall fungal colonisation, colonisation in multiple sites, and colonisation from high-risk sites. The incidence of systemic fungal infection was significantly lower in group B compared to group A (RR: 0.233; 95% CI: 0.113–0.447). Prophylactic fluconazole was shown to limit the severity and intensity of fungal colonisation as well as reduce the rate of progression from colonisation to infection (RR: 0.369; 95% CI: 0.159–0.815). In colonised infants (n=159) overall mortality was significantly lower in group B (3.7% vs 18.1%: RR: 0.174; 95%CI: 0.039–0.778). These data suggest that prophylactic fluconazole significantly decreases the incidence of colonisation and systemic infection by *Candida* species in neonates < 1500 gm. Additionally, prophylactic fluconazole may also decrease the rates of progression from initial colonisation to massive colonisation and to systemic infection.

Cohen LS et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA 2006; 296: 499–507.

Although there is a pervasive clinical impression that pregnancy is a time of emotional well-being providing a relative protection against psychiatric disorder, there is little evidence to support this view.

A recent study investigated the risk of **relapse of clinical depression** in **pregnant women who discontinued antidepressants during pregnancy**. Pregnant women (*n*=201) were recruited from 3 centres. The primary outcome measure was relapse of major depression as defined as fulfilling *DSM-IV* criteria. Eighty-six (43%) of the women experienced a relapse of depression during their pregnancy. Of 82 women who continued their medication during pregnancy, 21 (26%) had a relapse, while 44 of 65 (69%) of women who had stopped taking their antidepressant relapsed. After adjustment for confounders, women who discontinued their antidepressants had a 5-fold increased risk for relapse of depression than women who continued treatment (hazard ratio: 5.0; 95%CI 2.8–9.1; *P*<0.001). No association was found between the risk of relapse and either race or type of antidepressant. Younger women and women with a longer history with more recurrent depressive illness were associated with higher rates of relapse. The authors conclude that pregnancy is not protective against depressive disorder and pregnant women with a history of depression risk relapse with antidepressant discontinuation.

Levinson-Castiel R et al. Neonatal Abstinence Syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. Arch Pediatr Adolesc Med 2006;160:173–176.

Treatment of depression during pregnancy requires consideration of the risk vs. benefit profile for both the mother and the developing infant. While **fetal exposure to serotonin reuptake inhibitors** (SSRIs) has not been associated with major congenital malformations, there is growing evidence that their use during pregnancy may produce a **neonatal abstinence syndrome**. A recent cohort study evaluated 60 term infants with prolonged *in utero* exposure to SSRIs. Neonatal abstinence syndrome (NAS) was assessed with the Finnegan score. Of the 60 neonates exposed to SSRIs in utero, 18 (30%) had NAS symptoms (eight severe and 10 mild). All non-exposed neonates (60/60) had normal Finnegan scores. Of the positive cases, the maximum mean daily Finnegan scores were recorded within 2 days after birth, although maximum individual scores were recorded as long as 4 days after birth. The most frequent symptoms were tremor, GI or sleep disturbances, hypertonicity, and high-pitched cry. No infant with symptoms required any treatment. Of the eight infants with severe NAS, six were exposed to paroxetine (Paxil), one to fluoxetine (Prozac), and one to citalopram (Celexa). Long-term effects of prolonged exposure to SSRIs , in neonates who develop severe symptoms, have yet to be determined.

Chambers CD et al. Selective serotonin reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. N Engl J Med. 2006;354:579–587, 636–638.

In addition to NAS, an association between **SSRI use during pregnancy** and the development of **Persistent Pulmonary Hypertension of the Newborn** (PPHN) has been reported, based on relatively few cases. A large case-control study examined the risk for neonatal PPHN within the Slone Epidemiology Birth Defects Study. The diagnosis of PPHN was confirmed in 377 subjects of 637 infants with PPHN and matched against 836 controls. The main outcome was the relationship between maternal use of SSRIs and PPHN and included citalopram, fluoxetine, paroxetine, and sertraline. Analysis revealed that overall, neither the use of antidepressants nor the use of SSRIs was associated with a significantly increased risk for PPHN. However, when the analysis was restricted to the use of these medications after the 20th week of pregnancy, there was a significant increase in PPHN with the use of any antidepressant (OR: 2.9, 95%CI 1.3–6.5) and the use of SSRIs in particular (OR: 5.1, 95%CI 1.9–13.3). The use of other psychotropic drugs did not affect the risk of PPHN and there were not enough cases to determine differences between individual SSRIs. Based on their data, the authors note that the risk for PPHN associated with the use of SSRIs after 20 wks gestation is approximately 1% and should be considered in decisions as to whether to continue the use of SSRIs during pregnancy.

Guillet R et al. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. Pediatrics 2006;117:e137-e142.

Patole S. Association of H2-blocker therapy and higher incidence of necrotizing enterocolitis: A case of excessive collateral damage? Pediatrics 2006;117:531-532.

A recent study investigated possible associations between the use of **H2-blockers** and the incidence of **Necrotising Enterocolitis** (NEC) in premature infants. Infants with birth weights between 401 and 1500 g were selected from the National Institute of Child Health and Human Development Neonatal Research Network very low birth weight registry. This case-controlled (one case and three matched controls) retrospective study applied conditional logistic regression to control for gender, site of birth (outborn vs inborn), Apgar score of < 7 at 5 minutes, and postnatal steroid use. The study included 787 reported cases of NEC. However, of the planned 2361 matched controls only 2357 were matched successfully. Therefore, 3144 observations were used in the logistic regression. The overall incidence of NEC was 7.1% (787 of 11,072). H2-blocker use was found to be associated with an increased risk of NEC [OR: 1.71 (95% CI: 1.34–2.19); *P*< 0.0001]. H2-blockers were started on average 18.9 ± 15.5 days before NEC (median of 14 days with a range of 2–76). The authors concluded that the use of H2-blocker therapy is associated with an increased risk of NEC. However, they caution that the use of H2-blockers may be a marker for clinical signs of fragility, inflammation, or other problems that contribute to NEC.

Editorial Comment: *The pervasive use of acid modifying drugs (H2-RA, proton pump inhibitors) in the neonatal period continues despite the fact that demonstration of an acidic pH (a pharmacologically-based prerequisite for their use and action) is seldom engaged as part of the drug/dose selection process. While these drugs have an apparent large therapeutic index in adults and older children, this may not be the case for immature infants where dose-exposure-response relationships can vary substantially from those in older infants and children as a consequence of development.*

Elbahlawan L et al. ß$_2$-adrenergic receptor polymorphisms in African American children with status asthmaticus. Pediatr Crit Care Med 2006;7:15-18.

Historically, **aminophylline** was commonly included in medications used for the treatment of **asthma** symptoms. Its routine use declined with the development of selective β_2–agonists that had less dosing complications and better safety profiles. A potentially renewed role for aminophylline in asthma therapy was suggested by a recent report testing the hypothesis that specific **β_2-adrenergic receptor** (β_2-AR) genotypes in African American children with status asthmaticus are associated with clinical response to β_2–agonist therapy. A total of 31 African American children with status asthmaticus were enrolled in this cohort study conducted at a tertiary care children's hospital. β_2-AR **polymorphisms** were determined from blood samples taken at admission. Main outcome measures included admission to the PICU, need for mechanical ventilation, the need for various therapies and length of stay. They found no differences between genotypes in the percentage of children admitted to the PICU, requiring mechanical ventilation, receiving terbutaline treatment, or length of stay. Interestingly, patients having a Gln/Gln genotype of the β_2-AR showed less improvement of symptoms with β_2–agonist therapy, but were associated with an increased use and response to the addition of aminophylline to their treatment regimen. The authors propose that patients with this particular β_2-AR genotype may have a lower β_2–agonist-stimulated cAMP response. They may benefit more from the action of aminophylline which bypasses the β_2-AR by increasing intracellular cAMP through its ability to inhibit phosphodiesterases. These results support the use of aminophylline in select asthmatic patients and further highlight the potential impact of pharmacogenomics in providing optimal individualised drug therapy.

Spencer TJ et al. PET study examining pharmacokinetics, detection and likeability, and dopamine transporter receptor occupancy of short- and long-acting oral methylphenidate. Am J Psychiatr 2006;163:387-395.

Current research indicates that **immediate release preparations of methylphenidate** (IRM) are associated with more robust subjective detection and likeability responses which may impart a higher **abuse potential** than sustained-release preparations. Twelve healthy adults were randomly assigned to receive single doses of IRM or an osmotic controlled-release formulation of methyphenidate (ORM) that produces a more gradual rise in plasma concentration. Doses were selected that were predicted to produce equivalent maximum serum concentrations (40 mg IRM; 90 mg ORM). Methylphenidate plasma levels and responses to detection/likeability questionnaires were obtained hourly for 10 hours after dosing on two separate occasions. Dopamine transporter receptor occupancy was measured at 1, 3, 5, and 7 hours after dosing using a carbon-ll labelled imaging agent and PET scanning. Similar maximum serum concentrations of methylphenidate and maximum CNS dopamine transporter occupancy were achieved with both preparations although the ORM required a longer time to reach these values. Measures of subject detection and likability/dislikability were statistically greater in the IRM- than ORM-treated patients for up to 6 hours after dosing. The authors conclude that the abuse potential of oral methylphenidate is influenced by the rate of delivery and not solely by the magnitude of the plasma concentration. They propose that the use of sustained release preparation may be equally efficacious in term of activity on dopamine transporters but may avoid the abuse associated with the more rapidly released formulations.

Health Canada recently released a call for the removal of an extended release form of **dextroamphetamine/amphetamine** used for the treatment of ADHD from the Canadian market due to safety information concerning the association of **sudden deaths**, heart-related deaths, and strokes in children and adults taking usual recommended doses[1]. Health Canada's decision came as a result of a review of safety information provided by the manufacturer, which indicated there were 20 international reports of sudden death in patients taking either the immediate-release or sustained release preparation. These deaths were not associated with overdose, misuse or abuse. Fourteen deaths occurred in children, and six in adults. There were 12 reports of stroke, two of which occurred in children. None of the reported deaths or strokes occurred in Canada. As a result of a similar report, a US Food and Drug Administration (FDA) advisory committee recommended that manufacturers of stimulants used to treat ADHD include written guides to patients and place prominent **warnings on the drug labels** regarding potentially dangerous cardiac effects of these drugs[2]. This warning has sparked intense debate over the use of these medications and the best way to disseminate information about potential risks of drug therapies. The AAP has responded to this advisory by posting a question and answer page on its website[3] that provides information for parents and patients taking these medications. The FDA is not planning to take any immediate action on the committee's recommendations, and to bring the same questions next month to the pediatric drug advisory committee.

[1]www.hc-sc.gc.ca/ahc-asc/media/advisories-avis
[2]www.fda.gov
[3]www.aap.org/family/safetypillsadhd.htm

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Future meetings

Readers may be interested in attending the following meetings which have a focus on different aspects of paediatric and perinatal drug therapy.

- 4th International Workshop on Paediatric Clinical Trials
  Toronto, Canada
  September 28-29, 2006
  email: imti.choonara@nottingham.ac.uk

- Neonatal and Paediatric Pharmacists Group 12th Annual Conference
  Harrogate, UK
  November 3-5, 2006
  email: info@profileproductions.co.uk