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Trends in Paediatric Pharmacology and Toxicology

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Schreiber MD *et al.* Inhaled nitric oxide in premature infants with the respiratory distress syndrome. N Engl J Med 2003; 349: 2099–2107.

Chronic lung disease is the primary long-term complication of premature birth. **Nitric oxide** (NO) attenuates pulmonary vascular disease, inflammation, and pulmonary hypertension in newborns with lung injury. Researchers at the University of Chicago conducted a randomised, double-blind, placebo-controlled study to test the hypothesis that the use of inhaled NO would decrease the incidence of chronic lung disease and death in premature infants with the respiratory distress syndrome (RDS) who were receiving mechanical ventilation. Premature infants (<34 weeks) with RDS were randomly assigned to receive inhaled NO or inhaled oxygen (as a placebo) for seven days. There were no significant differences in birth weight, ethnic distribution, APGAR scores or surfactant administration between treatment groups. Patients were also randomly assigned to receive intermittent mandatory (IMV) or high-frequency oscillatory (HFO) ventilation. Chronic lung disease was diagnosed by blinded investigators at 36 weeks of age. **Fewer infants in the nitric oxide group died or had chronic lung disease compared to the placebo group** (48.6% vs 63.7%; *P*=0.03). The overall incidence of intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) was not different between groups. However, **severe IVH and PVL was less in the nitric oxide-treated group**. There was no overall effect of type of ventilation on outcome, but analysis of data according to the type of ventilation showed a trend toward a decreased risk of death and chronic lung disease in the group receiving NO and IMV but not in the group receiving NO and HFO. The authors advocate the use of NO in premature infants with RDS to decrease the incidence of chronic lung disease.

[1]Bolanos CA *et al.* Methylphenidate treatment during pre- and periadolescence alters behavioral responses to emotional stimuli at adulthood. Biol Psychiatry 2003; 54: 1317–1329.

[2]Carlezon WA *et al.* Enduring behavioral effects of early exposure to methylphenidate in rats. Biol Psychiatry 2003; 54: 1330–1337.

Stimulants such as **methylphenidate** (MPH) and its derivatives are widely used for the treatment of **attention-deficit hyperactivity disorder**. Given the plasticity of the human brain and the known changes in brain anatomy and function that occurs with development, the chronic use of these medications during childhood and adolescence have the potential to cause **enduring behavioral adaptations**, including altered drug sensitivity. Two recent studies have addressed this issue using animal models. Researchers at the University of Texas Southwestern Medical Center[1] investigated the long-term behavioural consequences of chronic administration of MPH during pre- and peri-adolescent development by assessing their behaviour in response to a variety of emotional stimuli. MPH-treated animals were more sensitive to stressful situations, showed increased anxiety-like behaviours, and had enhanced plasma levels of cortisol. Chronic MPH exposure led to decreased sensitivity to rewarding stimuli and a hyper-responsiveness to aversive situations. In a separate study[2], the behavioural effects of early developmental exposure to MPH were compared to cocaine. Early exposure to either MPH or moderate cocaine doses made animals aversive to cocaine and made higher doses less rewarding. MPH was also shown to cause depression-like symptoms and reduce the ability of rats to habituate to new environments. With the caveat that animal studies do not always predict outcomes in humans, these studies raise concern that chronic treatment of children and adolescents with medications that alter synaptic transmission may have the potential to alter behavioural parameters later in life. With the increasing incidence of ADHD and pervasive treatment with stimulant medications over the last two decades, we may only now begin to realise the neurobehavioural effects of these drugs as children reach adulthood.

Editor's Note: *While TRENDS does not usually feature animal studies, these results are potentially compelling as paediatric practitioners consider a whole generation of children exposed chronically to psychoactive medications.*

Carl JC *et al.* Comparison of racemic albuterol and levalbuterol for the treatment of acute asthma. J Pediatr 2003; 143: 731–736.

Inhaled ß2 agonists are the mainstay for the treatment of acute bronchoconstriction and in combination with systemic corticosteroids, are the primary treatment for status asthmaticus. The predominant $ß_2$ agonist in current use is a racemic (50:50) mixture of the (R)- and (S)-enantiomer of albuterol (salbutamol). **Levalbuterol** (the (R)-enantiomer) demonstrates a 100-fold more potent $ß_2$-receptor binding than (S)-albuterol and is thought to be responsible for the bronchodilator effect of the racemate. The (S)-enantiomer has essentially no bronchodilator activity and has even been shown to promote eosinophil recruitment and degranulation leading to increased bronchoconstriction. While previous reports have demonstrated significant improvements in pulmonary function tests with levalbuterol, researchers at Case Western Reserve University sought to determine whether this translates into reduced hospital admissions. In a randomised, double-blind, controlled trial, subsequent hospital admission was compared in children aged 1 to 18 receiving 2.5 mg racemic albuterol or 1.25 mg levalbuterol every 20 minutes for a maximum of six doses for the treatment of acute asthma exacerbation. Hospitalisation rate was significantly lower in the levalbuterol group (36%) compared to the racemic albuterol group (43%, *P*=0.02). Hospital length of stay was not different between groups which was attributed to the already short hospital stay (<48 h) in most cases. No significant adverse effects were seen in either group. Heart rate, respiratory rate, and oxyhaemoglobin saturation were also not different between groups. Given this decline in hospitalisations by levalbuterol and taking into

account the increased cost of this drug (relative to albuterol), the authors projected a yearly savings of $175,000 at their institution.

Cho Ng *et al.* Adenosine infusion for the management of persistent pulmonary hypertension of the newborn. Pediatr Crit Care Med 2004; 5: 10–13.

Persistent pulmonary hypertension of the newborn (PPHN) is commonly seen in the neonatal intensive care units (NICU). Adenosine infusion has been recently proposed for the treatment of PPHN, specifically those neonates who partially respond to inhaled NO (iNO), to further improve oxygenation. A prospective, observational case series report done in 9 patients from a single level three NICU was conducted. The patients had a clinical diagnosis of PPHN, were on mechanical ventilation, and iNO at 20 PPM. A continuous infusion of adenosine at 50 µg/kg/min was given. The investigators examined peripheral arterial oxygenation saturation, arterial oxygen tension, invasive systemic arterial blood pressure, and pulmonary arterial pressure, estimated using echocardiography. Six of the nine patients showed significant improvement in arterial oxygenation and pulmonary arterial pressure. Thus, the researchers concluded the combined therapies of iNO and adenosine may be therapeutic in patients with PPHN. The authors suggested non-responders to adenosine infusion may be those neonates with irreversible lung disease.

Ilett KF *et al.* Use of nicotine patches in breast-feeding mothers: Transfer of nicotine and cotinine into human milk. Clin Pharmacol Ther 2003; 74: 525–535.

The detrimental impact of maternal smoking on the developing fetus is well appreciated and has prompted studies on the benefits of the nicotine patch during pregnancy. Results of short-term studies have shown similar maternal exposure to nicotine and cotinine during smoking and the use of the patch, as well as minimal effects on fetal hemodynamics. This line of investigation has been extended into the post-partum period in a recent study comparing the transfer of nicotine and cotinine to newborns via breast milk of women smokers on the nicotine patch. Serial milk samples from 15 lactating women smokers were assessed for nicotine and cotinine by HPLC over a 24 hour period when they were smoking and when they were stabilised on 21-mg/d, 14-mg/d, and 7-mg/d nicotine patches. Their results showed no difference in the concentration of nicotine or continine in breast milk between smoking and the 21-mg/d patch. However, there were significantly lower concentrations of these compounds in breast milk of mothers when on the 14-mg/d and the 7-mg/day patches with a similar trend observed when calculating the absolute infant dose. Milk intake did not differ across treatments. Interestingly, their data also show that over 75% of the infant dose of nicotine equivalents is derived from cotinine which is known to have minimal or no cardiovascular and endocrine effects in humans. The authors promote the use of the nicotine patch for smoking cessation in lactating women as a safer alternative than continued maternal smoking.

Peloso UC *et al.* Penicillin concentrations in sera and tonsils after intramuscular administration of benzathine penicillin G to children. Pediatr Infect Dis J. 2003; 22:1075–1078.

Benzathine penicillin G (PCN-G), a repository form of the antibiotic has been the drug of choice for the secondary **prevention of acute rheumatic fever (ARF)** for almost four decades. Researchers in Brazil sought to provide data on the subsequent PCN concentrations in tonsils and sera in order to provide insight to the optimal PCN-G schedule for protection against recurrences of ARF. 58 children between the ages of 4 and 12 years with chronic tonsillitis were enrolled in the study. The children received a dose of **IV PCN-G 40,000 IU/kg (maximum total dose 1,200,000 units)** either 1 day, 10 days, 14 days or 21 days prior to surgery. At surgery, blood and tonsil samples were obtained and PCN concentrations were determined. The serum PCN concentrations were: 0.080, 0.031, 0.023, and 0.014 µg/ml respectively while those for the tonsil tissue were: 0.023, 0.010, 0.007 and 0.002 µg/g respectively. These results indicate that the current treatment recommendations may not provide adequate time above the MIC in tonsils.

Card T *et al.* Antibiotic use and the development of Crohn's disease. Gut 2004; 53: 246–250.

There are few well-established **environmental determinants of Crohn's disease**. However, some retrospective observational studies have implicated antibiotic use in its aetiology. Researchers in the UK recently reported the results of a prospective study where incident cases were selected from a general practice research database. Data collected over 5 years on smoking, prescriptions, age, sex, and a variety of symptoms and diagnoses that might be indicative of occult Crohn's disease were analysed in 587 Crohn's disease cases and 1460 controls. They report that antibiotic use 2–5 years pre-diagnoses occurred in 71% of cases compared with 58% of controls. When adjusted for age, sex, smoking, and the use of other drugs, antibiotic use had an odds ratio of 1.32 (1.05–1.65). They were unable to show specificity to any subgroup of antibiotics and associations similar to those with antibiotics were observed with oral contraceptives, cardiovascular and neurological drugs. Despite evidence of a causal relationship, the authors concluded that antibiotics, by interfering with normal colonisation, may be one of the missing components in the aetiology of Crohn's disease.

Arends NJT *et al.* GH treatment and its effect on bone mineral density, bone maturation and growth in short children born small for gestational age: 3-year results of a randomized, controlled GH trial. Clin Endocrinol 2003; 59: 779–787.

Small for gestational age (SGA) can be defined as a birth weight less than the tenth percentile for gestational age. About 10% of children born SGA fail to show adequate catch up growth during the first 3 years of life. Changes in the **growth hormone** (GH)/IGF-1 axis in these infants have been previously described. Arends *et al.* attempted to evaluate the effects of GH in SGA children. The children were randomised into three groups: control, non-growth hormone deficit (NGD), or growth hormone deficient (GHD). Both the NGD and the GHD received a GH dose of 33µg/kg/day. The parameters examined were: bone age, height and bone mineral density (BMD), the influence of the severity of growth retardation at the start of the study, and the GH dose and its effect on target height gained. A total of 104 Dutch children were screened for possible enrolment (48 boys and 56 girls), 5 children of whom dropped out of the study for various reasons. The remaining 99 children all fulfilled the same inclusion criteria. Both the NGD and the GHD groups showed a significant increase in height when compared to the control group. The investigators then compared the data from the current study with those from a previous study using 33ug/kg/d or 66ug/kg/d of GH in prepubertal children with short stature. There were no observed differences in height between those receiving either of the GH doses. Furthermore, bone maturation during the first two years of the study increased, but slowed in the later year of the study. The ΔBA (bone age)/ΔCA (chronological age) ratio for the three years correlated significantly with final height. There were no differences in the height gained between the NGD and the GHD groups. Thus, the investigators concluded that three years of GH treatment in short children born SGA will result in normalisation of height during childhood.

Miller FG *et al.* Ethical issues concerning research in complementary and alternative medicine. JAMA 2004; 291: 599–604.

The use of **complementary and alternative medicine (CAM)** has increased in recent years. In 1992, the Office of Alternative Medicine at the National Institutes of Health was established by Congress. Despite considerable funding for this initiative (~$114.1 million), there is concern regarding insufficient research on the ethics of studying CAM treatments and also, too few randomised, double-blind, placebo-controlled trials (RCTs). Researchers have argued that RCTs distort the holistic therapeutic milieu of CAM therapy. Moreover, certain CAM interventions such as hypnotherapy do not lend themselves well to placebo control. The comparison of CAM to conventional therapy is further complicated by the fact that volunteers for studies frequently have strong opinions for either CAM or conventional therapy causing them to desire not to be blinded for receiving an alternate form of therapy.

Nevertheless, with the increased use of CAM treatment as well as the increased budgets to study these treatments, ethicists and researchers alike are forced to confront these issues to maximise information gained from this research.

Shah S *et al.* How do institutional review boards apply the federal risk and benefit standards for pediatric research. JAMA 2004; 291: 476–482

With an increase in pharmaceutical research in children, there has been a renewed effort to understand how various paediatric **Institutional Review Boards** (IRBs) apply the previously acknowledged vague Federal guidelines for research in children. Only three types of research categories are currently allowed in children: (1) studies that offer a prospect of direct benefit, (2) studies that do not offer a prospect of direct benefit but that pose only minimal risk, and (3) studies that do not offer a prospect of direct benefit and pose a minor increase over minimal risk. **Minimal risk** is further defined as the risk of harm or discomfort ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. However, neither **"direct benefit"** nor **"minor increase"** is defined in the guidelines. In order to analyse the possible variation of interpretation of these concepts, 188 IRB Chairpersons who routinely review paediatric research were asked 21 hypothetical questions to analyse how the Federal guidelines were being applied by each board. Additionally, demographic questions were asked of each chairperson. The researchers found wide variations in responses for the risks of various hypothetical procedures associated with paediatric pharmacologic research. Moreover, similar variability in the analysis of what constituted benefit to the study participant was discovered. Some IRBs even considered direct payment as a direct benefit to the subject. The authors of the study conclude that this wide variability among IRBs, could lead to both research that is excessively risky for subjects as well as arbitrarily preventing research which is valuable to society.

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