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Trends in Paediatric Pharmacology and Toxicology

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Einarson A *et al.* The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. BJOG 2004; 111: 940-943.

Ondanestron use during pregnancy does not appear to increase the risk of major malformations according to a prospective, comparative observational study conducted at The Hospital for Sick Children in Toronto. Ondansetron is not indicated for nausea and vomiting during pregnancy. However, it has been used as a "last resort" despite lack of safety data. This study compared the rate of major malformations among women exposed to ondansetron, other anti-emetics (diclectin, metoclopramide, phenothiazines and ginger), or a non-teratogen during pregnancy. Each of the three groups included 176 women who had called a pregnancy help line in Canada or Australia. Women taking ondansetron were less than 3 months pregnant at the time of the call. Follow-up was conducted 4–6 months post delivery using a standardised form. Information was verified by the infant's primary physician. The ondansetron group had a total of 169 (96.8%) live births, 5 (2.9%) miscarriages, and 2 (1.3%) therapeutic abortions. There were 6 (3.5%) major malformations and no stillbirths. The average gestational age at birth was 38.7 weeks and average birth weight was 3362 g. There were no significant differences in any of the outcomes measured or maternal characteristics between the three groups. Hypospadias, which fit criteria for major malformation, was increased in the ondansteron group when compared with general population although was not statistically significant. Although limited by sample size, these results support the safety of ondanestron in pregnancy but underscore the need for larger studies.

Van Meurs K *et al.* Is surfactant therapy beneficial in the treatment of the term newborn infant with congenital diaphragmatic hernia? J Pediatr 2004;145: 312-316.

Mortality rates for congenital diaphragmatic hernia (CDH) remain high in spite of improvements in surgical care and numerous therapeutic modalities. Caring for these infants is complicated by associated pulmonary hypertension and pulmonary hypoplasia that may be related to the morphological and biochemical immaturity of the lung. There is current controversy over the use of surfactant in infants with CDH who may have associated respiratory distress syndrome. In a recent study, 522 infants with CDH diagnosed prenatally were identified, all of whom were born $\geq$ 37 weeks gestation, without major anomalies, and had immediate respiratory distress in the delivery room. Surfactant replacement therapy was used in 192 (36.8%) of these infants. Demographics were similar except for race. There was increased use of vasopressors, inhaled vasodilators, sedation, paralysis, alkalinisation and postnatal steroids in the surfactant-treated group. The use of ECMO and incidence of chronic lung disease were higher and survival was lower in the surfactant group. Surfactant therapy was significantly correlated with lower survival even after adjustment for higher use of ECMO, inhaled nitric oxide, and postnatal steroids. Results of this study demonstrate that surfactant therapy provides no benefit in the treatment of term infants with isolated CDH and suggests that this treatment may lead to worse outcomes.

Barclay L. Nicotine patch may be more helpful than buproprion for adolescent smoking cessation. J Consult Clin Psychol 2004:72:729-735.

Studies investigating smoking cessation in adults have suggested that the nicotine patch in combination with buproprion offers the most effective therapy. To test whether these results could be generalised to adolescents, a randomised double-blind study was conducted in 211 teenagers, ages 15 to 18 years, that compared the success rates on smoking cessation between the nicotine patch alone and the nicotine patch plus extended release buproprion. Patients were selected if they smoked at least 10 cigarettes per day prior to the study and had failed at least one trial to quit smoking in the previous 6 months. During the study, the patients received weekly group counselling sessions and were required to quit smoking 2 weeks after counselling was begun. All patients received the nicotine patch, titrated to the amount of cigarettes previously smoked, in a tapering dose schedule for 8 weeks. One week before smoking cessation, participants began receiving either buproprion (150mg/day) or placebo that continued for 9 weeks. After 10 weeks, smoking abstinence was not significantly different between groups (23% in the bupropion group vs 28% in the placebo group). The abstinence scores decreased at 26 weeks to 7% in the bupropion group and 8% for the placebo group. Time to relapse was similar between groups. The authors conclude that combination treatment with buproprion and the nicotine patch does not improve smoking cessation in adolescents over that seen with the nicotine patch alone.

Schlienger, RG, Jick, SS, Meier CR. Inhaled corticosteroids and the risk of fractures in children and adolescents. Pediatrics 2004; 114:469-473.

Inhaled steroids are the treatment of choice for mild and more severe forms of asthma. Their therapeutic benefit is believed largely to be associated with topical anti-inflammatory effects. However, following inhalation, a portion of the administered dose is swallowed and absorbed, thereby increasing the potential risk for side effects associated with systemic exposure. A recent study investigated the effects of inhaled corticosteroids on the incidence of bone fractures. In this study, 3, 744 fracture cases and 21, 757 matched control subjects (ages 5 to 17 years) were enrolled. Current exposure to inhaled corticosteroids did not significantly increase the risk of fracture when compared to non-users with an adjusted odds ratio of 1.01 (95%CI: 0.90–1.13). Long term users also displayed no evidence of substantially increased

fracture risk (adjusted odds ratio=1.15; 95% CI 0.89–1.48). The risk of fracture did not differ between groups regardless of the specific inhaled steroids used (beclomethasone, budesonide or fluticasone). Additional analysis showed no increased fracture risk attributable to inhaled steroids in individuals taking both inhaled and oral agents (1.21; 95% CI 0.99–1.49). However, in patients who were exposed to oral corticosteroids alone, there was evidence of increased fracture risk with increasing duration of use (odds ratio 6.07; 95%CI 0.38–97.44). These results add further support to the long-term safety of inhaled corticosteriods in the treatment of moderate to severe asthma.

Seger DL. Flumazenil – treatment or toxin. J Toxicol 2004;42:209-216.

In a recent review, the risk:benefit ratio of flumazenil has been brought into question. Flumazenil is a competitive antagonist at the benzodiazepine receptor. It reverses the augmentation of GABA synaptic transmission by benzodiazepines (BZD) in a dose-dependent manner thereby reducing the inhibitory activity of this neurotransmitter. By reversing the CNS depressant effects of benzodiazepines, its administration has been purported to decrease the morbidity associated with supportive procedures such as endotracheal intubation, CT scans, lumbar punctures and urinary catheterisations. Flumazenil was initially considered safe since severe reactions were uncommon and usually attributed to the underlying condition or ingestion. More recent studies suggest that flumazenil, via direct or indirect effects, may actually be detrimental to patients by precipitating seizures and increasing the incidence of re-sedation, aspiration, and even death. Increased seizure risk is most pronounced in patients who received flumazenil after ingestion of a proconvulsant drug in addition to a BZD. Seizure risk was also high in patients with a history of seizures who received flumazenil for "oversedation" after BZD administration. Seizures have also been reported after flumazenil administration for the reversal of conscious sedation, supporting a theory that there may be a genetic propensity to seizures that are unmasked by this drug. Other conditions where seizures may be precipitated include head injuries, chronic BZD use, co-ingestion of BZD and tricyclic antidepressants and possibly, ingestion of pro-convulsants without BZDs. Several studies have also reported re-sedation occurring after an initial "awakening" period following flumazenil administration. In one study, partial awakening after flumazenil administration was associated with more frequent aspiration than in patients who were allowed to wake on their own. The authors conclude by questioning the presumed benefit of using flumazenil for transient awakening in patients who may be at increased risk for seizures and other conditions that may be precipitated by its administration. The authors do not discount the benefits of flumazenil administration in cases of iatrogenic overdose, significant ingestion and reversal of paradoxical BZD response. They suggest that the risk:benefit ratio of flumzenil administration be determined in each overdose since the indications for its use may be more limited than previously recognised.

Lawrence SE *et al.* Beneficial effects of raloxifene and tamoxifen in the treatment of pubertal gynaecomastia. J Pediatr 2004; 145:71-76.

Gynaecomastia is a relatively common problem among adolescent males that occurs at a time when self-image and awareness are heightened. Although most cases resolve spontaneously, those that are persistent require alternative management. Medical treatment has been aimed at altering the effective androgen/oestrogen ratio by the use of dihydrotestosterone, aromatase inhibitors and anti-oestrogens. A recent retrospective chart review assessed the efficacy of tamoxifen and raloxifen for the medical management of persistent pubertal gynaecomastia. Significant breast reduction was achieved with both medications. Improvement was seen in 86% of patients receiving raloxifen and 91% of patients receiving tamoxifen. More patients receiving raloxifen (86%) had a greater than 50% reduction in breast size as compared to those receiving tamoxifen (41%). There were no reported adverse effects and there were no clinically or statistically significant changes in baseline levels of LH, FSH, testosterone, oestradiol or hepatic transaminases. The authors postulate that oestrogen receptor antagonists may represent a safe and effective alternative to other medications in reducing the size of glandular tissue in patients with persistent pubertal gynaecomastia.

[1]Kafantaris V *et al.* Lithium treatment of acute mania in adolescents: A placebo-controlled discontinuation study. J Am Acad Child Adolesc Psychiatry 2004;43:984-993.

[2]Francis J *et al.* Lithium toxicity-induced wide-complex tachycardia in a pediatric patient. J Pediatr 2004;145:235-240.

[3]Cooper WO *et al.* New users of antipsychotic medications among children enrolled in TennCare. Arch Pediatr Adolesc Med 2004;158:753-759.

Lithium has long been regarded as an effective treatment for mania in adults. However, few well-controlled studies have been conducted to assess its efficacy for the treatment of children and adolescents despite its widespread use in this age-group. In a placebo-controlled discontinuation study, researchers examined the efficacy of lithium in the treatment of acute mania in adolescents[1]. Participants received open label treatment with lithium (mean serum level 0.99 mEq/L) for at least 4 weeks. Responders were randomly assigned to continue or discontinue lithium during a 2-week double-blind, placebo-controlled phase. A total of 100 patients comprised the intention to treat sample. Patients with psychotic features or aggression were significantly less likely to respond to lithium treatment than those without psychosis or aggression (20% and 60.3%, respectively); a finding attributed to a lack of tolerance to withdrawal of the adjunctive antipsychotic medication required by the protocol. Forty subjects responded to open lithium treatment and were randomly assigned to either continue lithium treatment or be switched to placebo. Ten out of 19 (52.6%) who were maintained on lithium experienced significant symptom exacerbation whereas 13 of 21 (61.9%) patients who were switched to placebo had symptoms. The difference between the two groups was not significant. Contrary to the author's expectations, lithium monotherapy was not effective in preventing symptom exacerbations. These results challenge the efficacy of lithium as a mood stabiliser in adolescents and highlight the need to investigate more precisely the role of this drug in this age group.

Conclusive evidence for the efficacy of lithium is necessary since its administration is not without potential toxic effects. A recent case report describes the development of a wide complex tachyarrythmia in a 10 year old male after an acute increase in his lithium dose[2]. He had a long-standing psychiatric history with several diagnoses and was taking multiple medications including methylphenidate, escitalopram, oxcarbazine, clonidine, depakote, levothyroxine and lithium. He presented with symptoms of chest pain, palpitations, diaphoresis, lightheadedness, vomiting and abdominal pain. His initial ECG was interpreted as a supraventricular rhythm with aberrant ventricular conduction that failed to respond to IV boluses of adenosine or lidocaine. His serum lithium level on initial presentation was 3.1 mEq/L (normal range: 0.5–1.5 mEq/L). His cardiac rhythm was subesequently determined to be ventricular tachycardia which slowed and narrowed following procainamide boluses and eventually abated after a continuous infusion of procainamide and aggressive hydration and alkalinisation aimed at reducing his lithium levels. After resolution of his arrhythmia, all of his medications except lithium were restarted without adverse sequela.

The need for well-controlled studies on the efficacy and safety of psychiatric medications in children and adolescents is not restricted to lithium. An analysis of children aged 2-18 years taken from a population of patients participating in the TennCare health system in Tenessee revealed that new users of antipsychotic medications nearly doubled from 1996-2001[3]. This increase occurred in spite of stable trends in both the study population and overall incidence of serious mental disorders. The increase was attributed to a substantial rise in the use of these medications for either ADHD or conduct and affective disorders. The authors suggest that the perceived safety, especially of the newer atypical antipsychotic agents, may lead providers to prescribe these medications more frequently than in the past for behavioural indications not strongly supported by results from controlled clinical trials. Although safer than older medications, newer antipsychotics are not without adverse effects that include weight gain,

diabetes, galactorrhoea and cardiovascular effects in addition to their toxic effects occurring after acute intentional or non-intentional ingestions.

Collectively, these studies underscore the importance of establishing clear therapeutic efficacy for these and related psychoactive medications prior to their widespread use in the paediatric population. The interaction of neuroactive agents with a developing nervous system must be considered in the context of both acute effects and potentially, more long-lasting effects on CNS functions (e.g. cognition, behaviour, adaptation).

Brooks WA *et al.* Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial. Lancet 2004;363:1683-1688.

Zinc is thought to act in the acute phase response to infection by augmenting several aspects of the immune response. Children with good zinc status may have a more robust **immune response** during periods of acute infections, thereby potentially reducing antibiotic exposure and hospital stay. In a double-blind placebo-controlled clinical trial, 270 children (2–23 months) diagnosed with severe **pneumonia** were randomised to receive a supplemental dose of elemental zinc (20 mg per day) or placebo, plus a standard antimicrobial regimen of parenteral ampicillin and gentamicin. Primary outcome measures were duration of severe pneumonia (respiratory rate > 50, retractions, oxygen saturations < 95%) and length of hospitalisation. At discharge, serum zinc concentrations were significantly elevated in both groups relative to admission but concentrations in the zinc-treated group were significantly greater than those receiving placebo. The authors report a reduction in all three criteria for severe pneumonia, as well as time of hospitalisation, for the children in the zinc-treated group. When children who had wheezing as a component of their symptoms were omitted from the analysis, differences between zinc and placebo groups were even greater for all clinical signs, overall duration of severe pneumonia, and time in hospital. Children aged 12 months or older were noted to have resolved their respiratory illness earlier than younger infants. No serious adverse events were reported in either group.

Savoca MR *et al.* The association of caffeinated beverages with blood pressure in adolescents. Arch Pediatr Adolesc Med 2004;158:473-477.

Due to the increasing prevalence of **hypertension** in the **adolescent population**, researchers at the Medical College of Georgia sought to assess the association between the consumption of **caffeinated beverages** and blood pressure in African American and white adolescents. Adolescents (n=154, 15–19 years of age) selected meals from a sodium-controlled diet plan to be consumed over a 3-day period. Participants were stratified into three caffeine-intake categories (0–50 mg/kg/d; 50–100 mg/kg/d; >100 mg/kg/d). A general linear model was used to assess the effects of race and caffeine intake on systolic and diastolic blood pressure while controlling for sex and body mass index. There was a significant association between body mass index and both systolic and diastolic blood pressure (P<0.001). Systolic blood pressure was higher in African–American adolescents in the highest caffeine-intake group when compared to the two lower intake groups whereas there were no differences between intake groups in white adolescents. The effect on diastolic blood pressure was less pronounced. The authors concluded that African Americans (who are known to have a higher risk for hypertension) may be more susceptible to the pressor effects of caffeine than other populations. Whether this represents a direct effect of caffeine or reflects differences in dietary and lifestyle changes remains to be elucidated.

[1]Moore TJ *et al.* Reported adverse event cases of methaemoglobinemia associated with benzocaine products. Arch Intern Med 2004;164:1192-1196.

[2]Odemis E *et al.* Toxic methaemoglobinemia due to prilocaine injection after circumcision. Int Pediatr 2004;19:96-97.

Methaemoglobinemia (MHb), characterised by abnormal levels of oxidised haemoglobin that cannot bind and transport oxygen, is most commonly caused by exposure to medications. Cyanosis can occur with methaemoglobin levels that exceed 10%. Coma and death may result from levels above 50%. **Benzocaine** and other **topical anaesthetics** employed in multiple products have been associated with MHb. Serious adverse event reports to the FDA (November, 1997 – March, 2002) were surveyed for reports involving a benzocaine product[1]. Cases were stratified by product type (e.g. spray, gel or solution) and whether MHb was involved. Of 198 adverse events associated with benzocaine, 132 (66.7%) involved definite or probable MHb. The spray form of benzocaine was implicated in 93.2% of methaemoglobinemia reports. Mucosa was specified as the site of benzocaine use in 100% of methaemoglobinemia cases where this information was available. A single spray was applied in 53.5% of the cases. While this study implicated the mucosal application of the spray form of benzocaine as a risk factor, a recent case report documents the development of cyanosis and MHb in three infants receiving subcutaneous injections of **prilocaine** (4–5 mg/kg) following its use for local anaesthesia prior to circumcision[2]. In these otherwise healthy infants with a negative birth history, cyanosis appeared at 60, 180, and 30 minutes after injections. Haemoglobin levels were 8.5 g/dl, 9 g/dl, and 10.9 g/dl and methaemoglobin levels were 20%, 29%, and 27% respectively. Collectively, these studies underscore the risk of toxic MHb after therapeutic administration of oxidising agents such as benzocaine and related compounds. Health care professionals are advised that MHb can be a difficult diagnosis to make, but is associated with specific signs and symptoms as methaemoglobin levels rise. Treatment involves 1–2 mg/kg intravenous administration of methylene blue.

Editor's Note: *Collectively, these reports herald a note of caution when selecting a topical anaesthetic agent, especially when used in infants. While amide compounds generally produce fewer hypersensitivity reactions than esters, structure-activity relationships alone may not be sufficient to predict the occurrence of methaemoglobinemia.*

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