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Trends in Paediatric Pharmacology and Toxicology

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Bhandari V et al. Morphine administration and short-term pulmonary outcomes among ventilated preterm infants. Pediatrics 2005; 116: 352–359.

In a recent study, investigators sought to determine whether preterm infants who received **morphine infusions during mechanical ventilation** have improved **ventilatory outcomes**. They evaluated the duration of ventilator or oxygen therapy, number of air leaks, and an overall incidence of chronic lung disease (CLD) in 898 preterm infants (gestational age = 23-33 wks) that were randomised to receive either placebo or morphine. Morphine was dosed at 10, 20 or 30 mcg/kg/h based on gestational age. Intermittent open label bolus doses of morphine were allowed in both groups. The patients received the study drug until they were weaned from the ventilator or for 14 days. They determined that the average duration of mechanical ventilation was significantly longer in the morphine group than the placebo group (7 days [range = 4–20 days] vs 6 days [range = 3–19 days]). Continuous morphine infusions did not increase the incidence of CLD. After controlling for factors that would independently predict worse respiratory outcomes, the investigators found that additional intermittent morphine was associated with increased air leaks and longer durations of high frequency ventilation, nasal CPAP, and oxygen therapy. They concluded that morphine infusions did not improve short-term pulmonary outcomes in ventilated preterm infants. This study provides evidence that intermittent morphine may be harmful when used to relieve pain and discomfort in preterm infants on ventilatory support related to lung immaturity. However, morphine infusions for pain control are appropriate for infants who require analgesia postoperatively.

James LP, Simpson PM, Farrar HC et al. Cytokines and toxicity in acetaminophen overdose. J Clin Pharmacol 2005; 45: 1–7.

Several **cytokines** have been reported to have **hepatoprotective** effects in animal models of **paracetamol toxicity**. Researchers investigated the relationships of cytokines and toxicity in 111 paediatric cases of paracetamol overdose (mean age 13.6 yy, range 0–18 yr). Patients were stratified by toxicity severity that was based on levels of hepatic transaminases. Levels of interleukin 6, interleukin 8, and monocyte chemoattractant protein 1(MCP-1) were higher in patients with serum alanine aminotransferase > 1000 IU/L. MCP-1 had the strongest association with toxicity. MCP-1 values were higher in patients with greater delays in N-acetylcysteine treatment and in patients with higher values of prothrombin time. MCP-1 elevation in paracetamol overdose may represent an innate, immunomodulary response of the liver to cellular injury. An understanding of the role of cytokines in paracetamol toxicity may promote development of more effective therapies.

Ohlsson A et al. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Rev Abstract 2004; July.

Patent ductus arteriosus (PDA) can complicate the clinical course of preterm infants and may increase the risk of bronchopulmonary dysplasia (BPD) or necrotising enterocolitis (NEC). Indomethacin, a non-selective cyclooxygenase (COX) inhibitor, is commonly used for either prophylactic or therapeutic ductal closure with an 80% closure rate. However, adverse side effects (e.g. reduced blood flow to the brain, kidneys, and gut; gastrointestinal haemorrhage; oliguria) have prompted investigation into alternative therapies. A Cochrane review that included eight studies and 509 patients compared the effectiveness of **ibuprofen** to **indomethacin** for the closure of PDA. Based on these studies, there was no statistically significant difference in efficacy between these drugs. However, ibuprofen appeared to reduce the risk of oliguria, while increasing the risk of chronic lung disease and pulmonary hypertension with prophylactic use.

[1]Jones RA et al. Randomized, controlled trial of dexamethasone in neonatal chronic lung disease: 13- to 17-year follow-up study: I. Neurologic, psychological and educational outcomes. Pediatrics 2005; 116: 370-378.

[2]Lodygensky GA et al. Structural and functional brain development after hydrocortisone treatment for neonatal chronic lung disease. Pediatrics 2005; 116: 1–7.

Bronchopulmonary dysplasia (BPD) is a frequent morbidity associated with very low birthweight (VLBW) infants. In the US, **cortico-steroids** have been the mainstay of treatment to prevent chronic lung disease. However, findings of increased incidence of **neurodevelopmental delay** and cerebral palsy in infants treated with corticosteroids led to the American Academy of Pediatrics (AAP) 2002 statement that the routine use of systemic steroids in chronically ventilated VLBW infants is not recommended. More recent research suggests that corticosteroids may not adversely affect neurodevelopment as previously believed. In a large randomised controlled trial, 287 chronic oxygen dependent infants from 31 centres received either **dexamethasone** base (0.5 mg/kg/day for one week) or saline[1]. The investigators were able to fully evaluate 150 of the 195 surviving infants over a 13 to 17 year follow-up. Although disability and educational difficulties were high, there were no statistical differences between the dexamethasone and placebo groups. The authors urged the cautious use of dexamethasone therapy until other additional long term trials have been completed. A related study evaluated the potential effect of **hydrocortisone** on preterm brain development in patients with BPD[2]. A total of 61 infants were enrolled: 25 preterm (less than 32 weeks estimated gestational age with birth

weight less than 1500 g) treated with hydrocortisone (5 mg/kg/day tapered over minimum of 3 weeks); 35 untreated preterm infants; and 21 untreated term infants. Participants were followed and evaluated at up to 8 years of age. Three-dimensional MRI and Weshsler Intelligence Scales for Children-Revised (WISC-R) were used as outcome measures. Children who were treated with hydrocortisone were found to have similar volumes of grey matter, white matter, hippocampal volumes, cerebral spinal fluid, and WISC-R scores as those who were untreated when corrected for prematurity. The authors concluded that hydrocortisone appears to have no long-term effects on structural development or brain function and suggest that hydrocortisone may provide an alternative to dexamathasone in the treatment of chronic lung disease.

Rose PW et al. Chloramphenicol treatment for acute infective conjunctivitis in children in primary care: a randomized double-blind placebo-controlled trial. Lancet. 2005; 366: 37–43.

Topical antibiotics are commonly prescribed for treatment of **infective conjunctivitis** in the outpatient setting, although the support for this practice is lacking. A recent randomised, double-blind, placebo controlled trial compared the effectiveness of **chloramphenicol** eye drops in children with infective conjunctivitis. A total of 326 patients were enrolled (163 chloramphenicol treated; 163 placebo). Cultures were obtained for viral and bacterial pathogens. Parents applied drops 4 times daily (until 2 days after symptoms resolved) and recorded symptom severity at each dose. The primary outcome measure was cure rate at 7 days obtained from diaries completed by the parents. Participants were followed after 6 weeks to identify relapse. Pathogens were identified in 80% of children (67% bacterial; 3% viral; 10% both). Clinical cure by day 7 occurred in 128 (83%) of placebo-treated children compared to 140 (86%) receiving chloramphenicol (risk difference = 3.8%; C.I.: 4.1–11.8%). When considering only those children with bacterial infection, chloramphenicol still showed no significant improvement over placebo. Relapse rates were also similar between treatment groups. The authors conclude that the routine use of topical antibiotics is unwarranted and that most cases of either bacterial or viral conjunctivitis will improve without intervention.

Litalien C et al. Pharmacokinetics of proton pump inhibitors in children. Clin Pharmacokinet 2005; 44: 441–466.

The use of **proton pump inhibitors** has recently been extended to include treatment of paediatric acid related disorders. Lansoprazole has received FDA approval for use in paediatric patients greater than 1 year of age, while omeprazole is the only PPI approved for paediatric patients in Europe. Paediatric indications for PPI use include: gastro-oesophageal reflux, peptic esophagitis, peptic ulcers, H. pylori infections, and prevention of stress ulcers. They have also been used to decrease gastric acidity as a premedication for general anaesthesia and to improve the efficacy of pancreatic enzymes in cystic fibrosis patients. PPIs are acid labile prodrugs that must be absorbed systemically via the duodenum to enter the parietal cell and then diffuse into the extracellular canaliculus where they become ionised. The activated ionised form irreversibly inhibits the H^+/K^+ ATPase pump; the final pathway in gastric acid production. Even though the elimination half-life is very short (approximately 1 hour), these agents can be dosed once daily because of their irreversible covalent inhibition of the proton pump. *De Novo* synthesis is then required for restoration of acid secretion. PPI accumulation and activation are affected by pH. Therefore, elevation of the pH in the canaliculus by H_2-receptor antagonist such as ranitidine may shorten the period of PPI efficacy. Developmental considerations that may affect the use of PPIs in paediatric patients include the maturational expression of the proton pump itself and the expression of drug metabolising enzymes (i.e. CYP2C19 and CYP3A4). In general, paediatric patients between the ages of 1 and 4 y have increased metabolism of PPIs which may warrant more frequent dosing. Drug–drug interactions are more of a concern in patients who are CYP2C19 poor metabolisers because CYP3A4 metabolism would then predominate. As a class, PPIs appear to offer a safe and effective treatment for paediatric acid related disorders. Their use in combination with other acid suppressants (e.g. histamine-2 blockers) and prokinetic agents requires additional investigation.

Carmichael SL, Shaw GM, Laurent C et al. Arch Pediatr Adolesc Med 2005; 159: 957–962.

Hypospadias occurs due to the abnormal urethral closure around 8 to 14 weeks post-conceptional age. Previous reports have suggested that antenatal exposure to progestins in the first trimester may interfere with the production of fetal androgens leading to abnormal urethral closure. Newly developed natural progesterone products that are less androgenic and contain a lower dose have provided an alternative to those used previously. A large multicentre population-based, case-control study was performed to determine if the newer lower dose progestin formulations increased the risk of hypospadias. Hypospadias was defined as a second or third degree hypospadia with or without chordee. The analysis included 502 subjects diagnosed with hypospadias and 1286 live-born, non-malformed control subjects. Progestin exposure was reported by interview questionnaires. Forty-two (8.4%) case mothers and 31 (2.4%) controls reported having progestin exposure 4 weeks before or 14 weeks after conception. Adjusted odds ratios suggested progestin exposed mothers had at least a two-fold increase in risk of having an infant with hypospadias. Odds ratios for the month and type of progestin exposure did not alter the risk of hypospadias. The researchers concluded that exposure to newer progestins was associated with an increased risk of hypospadias and that the risk-benefit of their use be considered prior to treatment of fertility problems or pregnancy complications.

Berkenbosch JW et al. Prospective evaluation of dexmedetomidine for noninvasive procedural sedation in children. Pediatr Crit Care Med 2005; 6: 435–439.

Proper sedation for extended radiologic studies or other noninvasive procedures can be problematic in children. A recent prospective case series investigated the use of the α-2 adrenergic receptor agonist, dexmedetomidine, as an alternative agent for sedation in children. Forty-eight patients (6.9 ± 3.7 years) were given a bolus of 0.5–1.0 µg/kg over 5-10 minutes followed by an infusion of 0.5–1.0 µg/kg/h. Fifteen patients received dexmedetomidine after failing initial sedation with chloral hydrate ($n = 7$), midazolam ($n = 1$), or both ($n = 7$). Sedation was induced with an average dose of 0.92 µg/kg given over 10.3 ± 4.7 minutes and was maintained with infusions of 0.69 ± 0.32 µg/kg/h. Sedation scores of 3 ($n = 28$) and 4 ($n = 20$) obtained immediately before the procedure indicated deep sedation. There were significant decreases in heart rate and blood pressure ($P<0.001$), but neither decreased below the 5th percentile for age. There were statistically significant, but clinically unimportant, decreases in respiratory rate and SpO_2. No patient developed sinus pause, hypoxaemia or recovery-related agitation. The authors' suggestion that dexmedetomidine may be an effective alternative and/or rescue medication for sedation in children merits further study.

Hankins JS et al. Long-term hydroxyurea therapy for infants with sickle cell anemia: the HUSOFT extension study. Blood 2005; 106: 2269–2275.

Hydroxyurea is an anti-metabolite chemotherapy drug which has been shown to stimulate fetal haemoglobin production and help prevent vasoocclusive episodes in sickle cell disease. However, the long term efficacy and toxicity for infants remains unknown as does its role in preventing organ dysfunction. Hankins et al recently completed a 6 year study (the HUSOFT extension study) that investigated the long-term efficacy and toxicity of hydroxyurea in infants with sickle cell disease. Hydroxyurea doses were escalated to 30 mg/kg/d and patients were monitored with both laboratory testing and imaging studies. A total of 21 patients were enrolled in this study, 17 of which completed 4 years (yr) and 11 were treated for a total of 6 yr. The mean duration of therapy among the 21 patients enrolled in the extension study was 4.9 ± 1.3 yr (range, 2.1–6.0 yr). After 4 yr, hydroxyurea was associated with increased haemoglobin concentration, increased percentage of haemoglobin F, increased MCV, and decreased reticulocytes, white blood cells and platelets. Patients also experienced less episodes of acute chest syndrome

and had better splenic function. Rates of painful crisis were not affected. Patients did commonly experience mild to moderate neutropenia as well as several episodes of thrombocytopenia which resolved after temporary dose reduction. The authors concluded that infants with sickle cell disease tolerate prolonged hydroxyurea therapy well with sustained haematologic benefit, fewer episodes of acute chest and possible preservation of organ function.

Stelmach I et al. Effects of montelukast treatment on clinical and inflammatory variables in patients with cystic fibrosis. Ann Allergy Asthma Immunol 2005; 95: 372–380.

Inflamation contributes to progressive lung tissue damage in cystic fibrosis (CF). Cysteinyl leukotrienes have been shown to cause airway hyperresponsiveness and have been found in the sputum of patients with CF at concentrations sufficient to cause biological effects. Stelmach et al. studied 26 patients with CF, aged 6 to 18 years in a 20 week, randomised, double-blind, placebo controlled crossover trial to evaluate the effect of anti-inflammatory treatment with montelukast sodium. Patients received montelukast or placebo for 8 weeks in addition to their regular CF treatment. These investigators found that montelukast treatment significantly improved FEV1, PEF and FEF between 25% and 75% and also, significantly decreased cough and wheezing scale scores (P<0.001 for all). They also found that montelukast treatment was associated with decreased serum and sputum levels of eosinophil cationic protein and IL-8, decreased sputum levels of myeloperoxidase and increased serum and sputum levels of IL-10 (P<0.001 for all). The results of this study suggest that montelukast has measurable anti-inflammatory activity in patients with CF and that daily use of this medication may play an important role in the long term treatment of CF.

Dormer RL et al. Sildenafil (Viagra) corrects ΔF508-CFTR location in nasal epithelial cells from patients with cystic fibrosis. Thorax 2005; 60: 55–59.

Another potential role for the PDE5 inhibitor sildenafil (in addition to erectile dysfunction, pulmonary hypertension) resides with its apparent ability to modulate protein trafficking in patients with cystic fibrosis (CF). Airway epithelial cells were obtained from six individuals with CF and three non-CF controls, cultured and exposed *in vitro* to sildenafil for 2 hours. Drug exposure resulted in recruitment of ΔF508-CFTR (cystic fibrosis transmembrane conductance regulator) from a site close to the nucleus of the cell to the apical membrane with consequent restoration of sodium transport. Sildenafil also increased ΔF508-CFTR trafficking in cells from patients with CF who had a single copy of ΔF508 or a newly described CF trafficking mutation (R1283M). In non-CF controls, sildenafil did not influence CFTR location or function. The authors indicated that these preliminary results provide proof of principle for sildenafil to modulate ΔF508-CFTR trafficking and potentially, correct the "defect" in CFTR by altering cellular function in the airway.

Kim IK et al. Helium/oxygen-driven albuterol nebulization in the treatment of children with moderate to severe asthma exacerbations: A randomized, controlled trial. Pediatrics 2005; 116: 1127–1133.

Although helium/oxygen (heliox) alone may not be beneficial for acute asthma therapy, its lower gas density may lead to decreased flow resistance and increased aerosol penetration into the lungs. A recent study evaluated the efficacy of heliox vs. oxygen in driving continuous salbutamol nebulisation in children with moderate to severe asthma. Thirty children (2–18 yr) were ultimately enrolled in this randomised, controlled, single-blind trial. All children received an initial nebulised salbutamol treatment driven by 100% oxygen and a dose of oral corticosteroid. Patients were subsequently randomised to receive continuously nebulised salbutamol (15 mg/h) delivered with either heliox or oxygen using a non-rebreathing facemask. A composite (PI) score based on respiratory rate, wheezing, accessory respiratory muscle use, inspiratory/expiratory ratio, and pulse oximetry was the primary outcome measure assigned by a single blinded investigator observing a video recording. The mean change in PI score from baseline to 240 minutes was 6.67 for the heliox group compared with 3.33 for the oxygen group (P<0.001). Two-way ANOVA showed evidence of both a group main effect as well as interaction between time and group (P<0.001). Additional data suggested that children receiving the heliox were more likely to be discharged from the emergency department and that if they were admitted, their hospital stay was shorter than those receiving oxygen therapy. The authors suggest that heliox may serve a future role as adjunct therapy for moderate to severe asthma exacerbations in paediatric patients.

FDA. Statement on adderall-sudden death in children. J Pediatr Pharmacol Ther 2004; 4: 283.

A review of cases from the FDA Adverse Event Reporting System for 1999–2003 found 12 reports of sudden death in paediatric patients 1–18 years of age who were being treated for ADHD with Adderall (amphetamine/ dextroamphetamine) and Adderall XR. Five of these deaths were in children with described cardiac risk factor(s). One case had a family history of dysrhythmia and one had engaged in very rigorous exercise. Unexplained toxic levels during therapeutic dosing were also noted in two cases. The FDA has not recommended immediate changes in approved use of the drugs nor labelling but continued evaluation will assess new data.

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Paediatric and Perinatal Drug Therapy

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