Trends in Paediatric Pharmacology and Toxicology

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Camfield P, Camfield C. The frequency of intractable seizures after stopping AEDs in seizure-free children with epilepsy. Neurology 2005; 64: 973–975.

The development of **intractable seizures**, unresponsive to antiepileptic drugs (AEDs), is a potential concern when discontinuing treatment of seizure disorders in children. A recent study examined the prevalence of intractable epilepsy following **discontinuation of AED treatment** in a population based cohort of children with epilepsy. Seventy one percent (260/367) of eligible children were seizure free after 1 to 4 years of AED treatment and therapy was discontinued. One hundred and seventy one patients (66%) remained seizure free, while 79 children (30%) had at least one recurrent seizure and were restarted on AEDs. Three patients (1.15%) with recurring seizures developed intractable epilepsy. Results suggest that the occurrence of intractable epilepsy after discontinuing AEDs is rare. Whether the discontinuation of the AEDs contributed to the development of intractable epilepsy or whether it would have developed regardless of continued therapy, remains to be elucidated. As with initiation of AED therapy after seizure onset, the adverse effects of continued exposure to AEDs must be weighed carefully against the possible progression of the disease.

Dennery PA. Metalloporphyrins for the treatment of neonatal jaundice. Curr Opin Pediatr 2005; 17: 167–169.

Neonatal jaundice is commonly seen in the first week of life. Current treatments for hyperbilirubinaemia are directed towards reducing bilirubin after its formation. The **metalloporphyrins** are thought to inhibit haeme oxygenase responsible for the formation of bilirubin, thereby decreasing toxicity secondary to reducing bilirubin accumulation. A current review evaluated the use of metallophorphyrins for the treatment of neonatal jaundice. The only metalloporphyrin used in human trials is Tin mesoporphyrin (SnMP). The first report of the use of SnMP was in 1988 where it was shown to decrease bilirubin levels in 53 ABO-incompatible, Coombs-positive infants. The only adverse side effect reported during the trial was erythema that occurred when SnMP was used simultaneously with phototherapy. Another study published in 1994 used SnMP to treat near-term infants with hyperbilirubinaemia. They demonstrated a dose-dependent improvement in hyperbilirubin-aemia that decreased the peak plasma bilirubin concentration by 41% and reduced the need for phototherapy by 76%. The only side effect reported in this study was transient erythema. In a subsequent study conducted in 1998, SnMP effectively reduced peak bilirubin levels in infants with G6PD deficiency when compared to controls. An Argentinian study conducted in 1999, found the need for phototherapy was eliminated in eight infants with bilirubin levels between 15 and 18 mg/dl after treatment. The remaining studies in the literature consist of case reports which also support the efficacy of SnMP in reducing peak bilirubin concentrations. Collectively, these studies provide evidence in support of the use of SnMP to reduce the need for phototherapy and potential exchange transfusions. However, the pharmacokinetics and safety of SnMP have not, to date, been completely characterised.

Wheeler DS *et al.* Theophylline versus terbutaline in treating crticially ill children with status asthmaticus: A prospective randomised, controlled trial. Pediatr Crit Care Med 2005; 6: 142–147.

Theophylline's role in the treatment of **critically ill** paediatric asthmatics was examined in a recent study of 40 critically ill children, ages 3–15 yr, with **asthma** induced respiratory failure. All children received standard doses of intravenous methylprednisolone (2 mg/kg/every 6 hours for 24 hours followed by 1 mg/kg every 6 hours until discharge from the PICU) and continuous salbutamol nebulisation administered at a rate of 10 mg/h. Eligible children were then randomised to one of three study groups; theophylline + placebo, terbutaline + placebo, or theophylline + terbutaline. The primary outcome variable was the change in clinical asthma score (CAS) over time. Secondary outcome variables included length of time to a CAS ≤ 3, length of stay in the PICU, progression to mechanical ventilations, and incidence of adverse events. No differences in outcome variables were observed with the exception of increased nausea in the children randomised to theophylline + terbutaline. The authors concluded that theophylline, when added to continuous nebulised salbutamol therapy and intravenous corticosteroids, is as effective as terbutaline in treating critically ill children with status asthmaticus. In addition, theophylline is significantly less expensive than terbutaline even when the cost of monitoring serum theophylline levels is included.

[1]Moya F *et al.* A multicenter, randomised, masked, comparison trial of lucinactant, cofosceril palmitate, and beractant for the prevention of respiratory distress syndrome among very preterm infants. Pediatrics 2005; 115: 1018–1029.

[2]Sinha S *et al.* A multicenter, randomised, controlled trial of lucinactant versus poractant alfa among very premature infants at high risk for respiratory distress syndrome. Pediatrics 2005; 115: 1030-1038.

[3]Wilson D *et al.* Effect of exogenous surfactant (Calfactant) in pediatric acute lung injury. A randomised controlled trial. JAMA 2005; 293: 470–476.

There are a variety of **surfactants**, synthetic and animal-derived, currently available for **Respiratory Distress Syndrome** (RDS) in preterm infants. Surfactants have also been studied for use in adult and paediatric acute respiratory distress syndrome (ARDS). Human surfactant contains 70–80% phospholipids, ~10% neutral lipids, and ~10% proteins.

The major surface-active component in surfactant is dipalmitoylphosphatidylcholine (DPPC). There are four apoproteins (SP-A, SP-B, SP-C, SP-D) in surfactant which enhance spreadability and surface adsorption. SP-B is thought to be the most critical protein for surfactant activity.

Calfactant (Infasurf®) is a natural surfactant from calves' lungs. Calfactant contains natural DPPC and proteins SP-B (40%) and SP-C. Colfsceril Palmitate (Exosurf®) is a synthetic surfactant which contains synthetic DPPC, cetyl alcohol to enhance surface activity, and tyloxapol to enhance spreading and adsorption. It contains no apoproteins. Beractant (Survanta®) is a modified natural surfactant from bovine lung. Beractant contains natural SP-B (<0.5%) and SP-C proteins as well as DPPC. Poractant (Curosurf®) is a natural surfactant from porcine lungs which contains natural DPPC and proteins SP-B and SP-C.

Two multicentre, randomised, controlled clinical trials[1,2] compared Lucinactant (new synthetic surfactant) to Colfosceril Palmitate, Beractant and Poractant. Lucinactant was significantly better than Colfosceril (39.1% vs 47.2%; odds ratio: 0.68; 95% confidence interval: 0.52–0.89), but not Beractant, at preventing RDS at 24 hours of life. Interestingly, Lucinactant was significantly better than Colfosceril (4.7% vs 9.4%; OR: 0.43; 95%CI: 0.25–0.73) and Beractant (10.5%; OR: 0.35; 95% CI: 0.18–0.66) for decreasing mortality at 14 days. At 36 weeks postmenstrual age (PMA), Lucinactant significantly decreased the rate of BPD compared to Colfosceril and Beractant. There was no statistically significant difference between Lucinactant and Poractant for survival outcome measures. Survival without BPD at 36 weeks PMA was 64.7% versus 66.9% for the Lucinactant and Poractant groups respectively. When compared to Poractant, Lucinactant had comparable safety and efficacy in preventing and treating RDS.

Three previous prospective, randomised controlled clinical trials of surfactant [Exosurf, Beractant, Venticute (German product)] replacement therapy in adult with **ARDS** showed little or no benefit. Wilson *et al.*[3] speculated that a natural surfactant with higher levels of SP-B might prove effective in paediatric ARDS. A multicentre, randomised, blinded trial of Calfactant compared to placebo was conducted in 153 paediatric patients. The main outcome measures were ventilator free days and mortality. There was no difference in ventilator free days between the two groups; however, there was a statistically significant increase in mortality in the placebo group (27/75 vs 15/77; odds ratio, 2.32; 95% CI: 1.15–4.85). A significant decrease in the oxygenation index from 20 in the placebo group to 13.9 in the Calfactant group occurred after 12 hours.

Dugas MA *et al.* Fluticasone inhalation in moderate cases of bronchopulmonary dysplasia. Pediatrics 2005; 115: 566–572.

Inflammation is thought to be an important factor in the development of bronchopulmonary dysplasia (BPD) in premature infants. Systemic corticosteroids (primarily dexamethasone) have been widely used for the treatment and prevention of BPD. However, systemic steroids have been implicated in adverse neurodevelopmental outcomes which have more recently limited their use. The safety and clinical efficacy of inhaled corticosteroids in BPD has not been established. A randomised controlled trial was designed to determine the efficacy of fluticasone on weaning oxygen therapy in preterm infants. Thirty two infants ≤ 32 weeks gestation with moderate BPD requiring supplemental oxygen at 28–60 days of postnatal age were included in the study. Treated infants weighing between 500 and 1200 grams received inhaled fluticasone 125 mcg twice daily for 3 weeks and once daily during the fourth week. Dosage was doubled for infants >1200 grams. Primary outcomes measured were the mean difference in duration of oxygen supplementation among the treated and placebo groups and difference in survival without supplemental oxygen at the end of the treatment period (28 days). Secondary outcomes measured were effect on duration of ventilator support, blood glucose, arterial pressure, diuresis, growth, cortisol axis, chest radiograph scores, and length of hospital stay. The study found no difference in the duration of oxygen use, ventilator support, or the length of hospital stay between fluticasone and placebo treated infants. Treated patients did show a trend toward lower chest radiograph scores, higher systolic blood pressure, and lower cortisol/creatinine ratios. Results of this study suggest that the use of inhaled corticosteroids is not an effective alternative for the treatment of oxygen dependent infants with moderately severe BPD.

Moolchan ET *et al.* Safety and efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. Pediatrics 2005; 115: 407–414.

The prevalence of adolescent smoking remains high. Most adolescent smokers continue to smoke into adulthood incurring both short and long term adverse effects. A large portion of adolescents have unsuccessfully tried to stop smoking at least once. Very few pharmacological interventions have been evaluated for smoking cessation in adolescents. Recently, a randomised controlled clinical trial was conducted to determine the safety and efficacy of the nicotine patch and gum in adolescents. A total of 120 patients, ages 13–17 years, were randomised to one of three groups; active patch and placebo gum, active gum and placebo patch, placebo gum and placebo patch. Dosages were determined by weight and number of cigarettes per day. All patients smoked ≥ 10 cigarettes per day, and scored ≥ 5 on the Fagerstrom Test of Nicotine Dependence. Patient population was 72% white and 70% female. Interventions were made after 12 weeks of nicotine treatment and cognitive behavioural therapy and a 6 month follow up visit. Safety was assessed based on reports of adverse events. Compliance was higher for the patch (mean 78.4–82.8%) than for the gum (38.5–50.7%). Adverse events were similar to those reported in adult studies. Abstinence from smoking was verified with exhaled carbon monoxide levels of ≤ 6ppm in the intent to treat analysis. The nicotine patch was more effective than placebo (18% vs 2.5% respectively) as an adjunct to behavioural therapy. The authors also reported a trend toward higher abstinence rates in the patch group compared with the placebo group sustained at the 3 month follow up. There was no significant effect of patch versus gum (18% vs 6.5%) or gum versus placebo (6.5% vs 2.5%) on cessation outcomes. The authors concluded that nicotine patch therapy in combination with cognitive-behavioural intervention was effective, compared to placebo, in treating adolescent smokers. Larger studies are needed to assess the efficacy of nicotine gum in the adolescent population.

Schaaf HS *et al.* Isoniazid pharmacokinetics in children treated for respiratory tuberculosis. Arch Dis Child 2005; 90: 614–618.

Due to its powerful bactericidal activity against metabolically active mycobaccili, **isoniazid** (INH) remains the cornerstone of treatment for active tuberculosis. Prolonged exposure of organisms to concentrations above the minimum inhibitory concentration leads to bacteriolysis. In adults, the **N-acetyltransferase 2** (NAT2) genotype is known to be responsible for the fast (FF), intermediate (FS), and slow (SS) metabolism of INH found in the general population. Although metabolism of INH has been reported to be faster in **children** relative to adults, studies in children have not accounted for acetylator genotype. To define the pharmacokinetics of INH in children with tuberculosis in relation to the NAT2 genotype, the elimination rate constant (k) and area under the concentration time curve (AUC) were determined in 64 children < 13 years with concomitant determination of acetylator genotype. As expected, mean k values were significantly different between acetylator genotypes [SS (0.254 ± 0.046); FS (0.513 ± 0.074); FF (0.653 ± 0.117)]. When compared within each genotype, there was a significant decrease in k with age. Comparisons with ethnically similar adults showed that mean concentrations of INH for each genotype were significantly higher than the respective genotype in children. The authors conclude that younger children eliminate INH faster than older children and children, as a group, eliminate INH faster than adults and thereby require a higher weight-based dose to achieve comparable serum concentrations. An accompanying editorial highlights the observation that, in addition to requiring higher INH doses, this study also demonstrates that children are as metabolically heterogenous as adults.

Editor's Note: While it is more common to think of children as having immature and developing metabolic capacity, this article provides one of several examples where drug metabolism in children is actually faster than in adults; a difference that appears to occur independent of genotype and to be of potential clinical significance with respect to drug exposure and efficacy.

Hankins JS *et al.* Long-term hydroxyurea therapy for infants with sickle cell anemia – the Husoft extension study. Blood 2005 [epub ahead of print].

The advantages of **hydroxyurea** for the treatment of **sickle cell disease** (fewer episodes of vaso-occlusive painful crises, fewer hospitalisations, and fewer episodes of acute chest syndrome) have been recognised for almost a decade. However, the long term effect of this drug, especially in **children**, is not well defined. Initial results from the Hydroxyurea Safety and Organ Toxicity trial in infants enrolled at 6-24 months of age and followed until two years, showed that daily treatment with hydroxyurea led to elevated haemoglobin concentration and percent fetal haemoglobin and prevented loss of spleen function. Twenty one of these patients were enrolled in an extension of this study. Of these, 17 completed four years of hydroxyurea, and six completed six years. Compared with historic controls, hydroxyurea-treated patients had increased haemoglobin concentrations, percent fetal haemoglobin, and MCV and decreased reticulocytes, WBC, and platelets. They also experienced significantly fewer acute chest syndrome events (7.5 vs 24.5 events/100 person-years; $P < 0.001$) and had better spleen function and growth rates. Toxicity was generally mild with no cases of creatinine or liver enzyme elevation, myelodysplasia, or cancer. While the authors acknowledge the need for close monitoring for toxicity, these results suggest that long term treatment of infants with hydroxyurea may be both safe and effective.

Chicella MF *et al.* Prokinetic drug therapy in children: a review of current options. Ann Pharmacother 2005; 39: 706–711.

The mainstay of treatment of gastroesophageal reflux disease (GERD) in children has been acid suppression. In cases of refractory symptoms, prokinetic agents (i.e. **metoclopramide** and **erythromycin**) are frequently added. A recent article reviewed the pharmacology, safety, and efficacy of these drugs in paediatric patients with GERD. Nine articles on metoclopramide and twelve articles on erythromycin were evaluated. Seven of nine studies comparing metoclopramide with placebo or another prokinetic agent showed no significant improvement in symptoms. Safety was a concern with metoclopramide use due to extrapyramidal adverse events including dystonia and tardive dyskinesia. Alternatively, several observational reports and controlled trials demonstrated improved feeding tolerance in children taking erythromycin. Although there has been some concern for an increased incidence of infantile hypertrophic pyloric stenosis (IHPS) with perinatal erythromycin use, the authors report that treatment related adverse events were uncommon. The authors advocate the use of erythromycin for the treatment of paediatric GERD if a prokinetic agent is required. Furthermore they suggest that, given the lack of prospective controlled studies demonstrating metoclopramide's efficacy and safety, it should not be considered a treatment option.

Papacci P *et al.* Use of intravenous ketorolac in the neonate and premature babies. Pediatr Anesth 2004; 14: 487–492.

Typically, opioid analgesics are used to treat neonatal pain; however, concerns related to respiratory depression limit the use of opioids in some situations. **Ketorolac tromethamine**, a potent nonsteroidal anti-inflammatory analgesic, has been shown to be effective in the treatment of **moderate to severe pain** in adults and children but not in neonates. Papacci et al conducted a study to evaluate the safety and efficacy of ketorolac in 18 **premature neonates** with pain related to surgery (*n*=12), invasive procedures (*n*=5), or epidermolysis bullosa (*n*=1). Ketorolac 1 mg per kg was given via intravenous infusion over 10 minutes. Ketorolac was given either as a single analgesic or for break through pain with caudal block. All the patients had bronchopulmonary dysplasia but were breathing spontaneously. Eight patients were oxygen dependent (FiO_2 0.25–0.35) and 11 were on furosemide and theophylline. None of the neonates experienced haematologic complications as monitored by WBC, neutrophils, haematocrit, platelets, PT, aPTT, and fibrinogen. There were no significant changes in renal or hepatic function before treatment or post treatment. There were no signs of gastric, renal, or wound bleeding complications in any of the patients. There were no signs of intraparenchymal or peri-intraventricular bleeding before treatment or 24 hours after treatment as assessed by head ultrasound. Efficacy was assessed using the Neonatal Infant Pain Scale (NIPS). Pain scores were determined before ketorolac administration and then at 30 min, 2 and 6 hours after administration. Seventeen patients (94%) had statistically significant reductions in the pain score at all time points after treatment. There were no differences in pain scores between any of the post-dose assessments. Results of this observational study suggest keterolac may be an effective treatment of pain in neonates but pharmacokinetic studies in this population are lacking.

Carbajal R *et al.* Morphine does not provide adequate analgesia for acute procedural pain among preterm neonates. Pediatr 2005; 115: 1494–1500.

In contrast with historic views to the contrary, recent data indicate that **preterm infants** are able to experience **pain** and may even be hypersensitive. Furthermore, there is increasing evidence that repeated pain exposure causes hyperalgesia that may result in long-term changes in pain processing during development. Continuous **morphine** infusions are commonly used for ongoing analgesia during routine NICU care and invasive procedures in ventilated preterm neonates despite limited data on its efficacy and safety. A recent prospective, randomised, double-blind, placebo-controlled study investigated the analgesic efficacy of intravenously administered morphine on heel stick-induced acute pain in preterm neonates. Neonates received a loading dose (100 µg/kg) followed by continuous infusion (10–30 µg/kg/h) of morphine (*n*=21) or placebo (5% dextrose) infusions (*n*=21). Pain was assessed using the Douleur Aigue Nouveau-ne (DAN) scale and the Premature Infant Pain Profile (PIPP) before the loading dose and at 2–3 hours and 20–28 hours after the loading dose. Using the DAN scale (behavioural pain scale), no differences were seen within groups over time nor were there differences between morphine and placebo groups at any of the assessment times. With the PIPP scale (multidimensional pain scale), there was a significant decline in pain over time, but again, there were no differences between treatment groups. There was no correlation between pain scores and plasma morphine levels using either scale. The authors conclude that morphine does not provide adequate analgesia for preterm neonates < 33 weeks gestation exposed to acute pain. However, they are careful to note that their conclusions do not apply to continuous severe pain, but rather suggest the need for additional analgesic approaches in treating acute procedural pain.

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