Paediatric and Perinatal Drug Therapy, 2003; 5 (4)

Trends in Paediatric Pharmacology and Toxicology

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Capparelli EV *et al.* Population pharmacokinetics and pharmacodynamics of zidovudine in HIV-infected infants and children. J Clin Pharmacol 2003; 43: 133–140.

Capparelli EV *et al.* Pharmacokinetics and tolerance of zidovudine in preterm infants. J Pediatr 2003; 142: 47–52.

Zidovudine (ZDV) was the first antiretroviral agent approved for the treatment of children with HIV and the first nucleoside monotherapy effective in preventing perinatal transmission of HIV. ZDV is eliminated through glucuronidation and to a lesser extent, it is excreted unchanged in the urine. In the newborn period, the ability to **glucuronidate** is greatly reduced. In adults, ZDV concentrations above 0.7 μM correlate with improved clinical response, while concentrations above 1.3 μM have been associated with higher haematologic toxicity. Therefore, maintaining levels within this narrow therapeutic range is essential. Researchers have found after studying 394 newborns that ZDV oral **clearance is directly proportional to gestational age** and is greatly reduced compared to older children. Previous studies had indicated that ZDV clearance was mature by the first two weeks of life. However, these researchers have discovered that it may take as long as the first two years of life for maturation. Further complicating this situation the researchers discovered that clearance varies over five fold for all age groups over the first 200 months of life.

***Editor's Note**: Based on this information, it would appear that the best approach to individualising AZT treatment in the neonate would be through routine therapeutic drug monitoring. However, extreme variability in UGT activity may obscure the relationship between age (UGT activity) – dose – plasma concentration making routine TDM difficult.*

Dorrington CL *et al.* The frequency of complications associated with the use of multiple-dose activated charcoal. Ann Emerg Med 2003; 41: 370–377.

Treatment with **multiple doses of activated charcoal (MDAC)** is frequently indicated to enhance the elimination of numerous toxins. Nevertheless, the only study that examined the utility of MDAC from 1984 demonstrated no benefit. Moreover, to date, there are eight cases of **fatal pulmonary aspiration** associated with MDAC in the literature. Therefore, researchers in Canada decided to investigate this area further through a retrospective chart review. Of the 878 patients who received MDAC (defined as more than two doses within a 12 hour period) only five had clinically significant pulmonary aspiration. Of these five patients, four did not have any long term sequelae while the fifth committed suicide before long term outcomes could be determined. None of the patients receiving MDAC suffered from **gastrointestinal obstruction**. Only 6% of patients had **sodium** >145 mmo/l while 0.6% had sodium >155 mmo/l. Only 0.3% of patients obtained a peak **magnesium** level greater than 3.75 mg/dl. Therefore, the researchers concluded that clinically significant sequelae are more rare than previously considered.

Hoffman TM *et al.* Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation 2003; 107: 996-1002.

For almost 30 years, multiple studies have documented the predictable fall in cardiac output after congenital heart surgery. The incidence of this decrease, commonly referred to as **low cardiac output syndrome (LCOS)** has been estimated at around 25%. Previously, the effects of a positive inotropic and vasodilatory agent such as **milrinone** had not been studied in children. Therefore, 238 patients at 31 centers in North America were randomised to 3 groups: placebo, low dose milrinone (25 μg/kg bolus over 60 minutes followed by a 0.25 μg/kg/min infusion) or high dose milrinone (75 μg/kg bolus over 60 minutes followed by a 0.75 μg/kg/min infusion). The incidence of LCOS was 25.9 %, 17.5% and 11.7% in these three groups respectively. This study indicates a **64% relative risk reduction** of LCOS with the prophylactic use of high-dose milrinone. There were no significant differences in the incidence of adverse events (e.g., hypotension, arrhythmia, and thrombocytopenia) with either dose of milrinone compared with placebo.

Gibb DM *et al.* Adherence to prescribed antiretroviral therapy in human immunodeficiency virus-infected children in the PENTA 5 trial. Pediatr Infect Dis J 2003; 22: 56-62.

Advances in **antiretroviral therapy (ART)** have significantly reduced early morbidity and mortality in children infected vertically. Nevertheless, these improvements are predicated on adherence to a difficult medication dosing schedule. Most previous studies on **antiretroviral compliance** were either retrospective or cross-sectional. However, a subanalysis of the recent **Paediatric European Network for Treatment of AIDS (PENTA) 5** trial, which evaluated different dual nucleoside reverse transcriptase inhibitor therapy combinations with and without the protease inhibitor Nelfinavir, evaluated compliance through a series of questionnaires completed at 4, 12, 24 and 48 weeks of therapy. Questionnaires were returned for 84% of children. Full adherence was reported in 74% of the questionnaires without a change over time. Children over the age of 10 with more symptomatic disease at the initiation of therapy were significantly more adherent to the therapy. Additionally children with greater compliance achieved a lower HIV RNA serum concentration.

Weiner DL *et al.* Preliminary assessment of inhaled nitric oxide for acute vaso-occulsive crisis in pediatric patients with sickle cell disease. JAMA 2003; 289: 1136-1142.

Vaso-occlusive crisis (VOC) is a frequent acute painful complication of **sickle cell disease (SCD)**, accounting for 90% of hospitalisations in children with SCD beyond early childhood. The pathophysiology of VOC is not completely

understood. However, abnormal interactions between HbS and vascular endothelium are thought to result in **dysregulation of vascular tone**. Despite advances in understanding of SCD, to date there are no effective approved therapies for acute VOC targeted at the mechanism of disease. Thus, previous treatment has been largely symptom directed. Researchers have hypothesised that **nitric oxide (NO)** might promise a mechanism of disease-based therapy for the treatment of VOC through improvement in vascular tone. 20 patients aged 10 to 21 were randomised to a prospective double-blind, placebo-controlled, clinical trial between 1999 and 2001 to receive NO (80 ppm) or placebo for four hours. Preliminary analysis demonstrated a significant reduction in the visual analog scale (VAS) for pain with NO therapy. Moreover, the NO group had a significant reduction in morphine requirements at 6 hours. Finally, the duration of hospitalisation was significantly reduced in the NO group. There was no significant difference in toxicity between the placebo group and the NO group.

Casper RC *et al.* Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy. J Pediatr 2003; 142: 402–408.

During their childbearing years, women have been found to be at greatest risk for having a major depressive disorder. Many women fear taking medications for their **depression** due to the possibility of both short and long term effects on their babies. Researchers sought to uncover if the children of mothers who were treated with **SSRIs** (N=31) were at risk for problems as compared to children of depressed mothers who remained medication free during pregnacy (*N*=13). The mothers in this study received sertraline, fluoxetine, paroxetine, and fluvoxamine. The children were followed to between 40 and 60 months of age. All children underwent neurologic and dysmorphology examinations. The study uncovered **significant differences in the APGAR** scores of exposed children (8.2 vs 7.0 and 9.0 vs 8.4 at one and five minutes, respectively) as well as the **psychomotor development** scores of the Bayley Scales of Infant Development, Second Edition (BSID-II). However, no differences were found in the mental developmental indices of the BSID-II. The authors conclude that while this non-randomised "pilot investigation" has many limitations, it warrants further investigation.

Canfield RL *et al.* Intellectual impairment in children with blood lead concentrations below 10 μg per deciliter. NEJM 2003; 348: 1517–1526.

Lead is known to be neurotoxic in young children. Previous studies had indicated that blood lead concentrations above 10 μg/dl (0.483 μmol/l) had **adverse cognitive effects**. This study of 172 children attempted to identify any changes in children's Stanford-Binet Intelligence Quotient **(IQ)** that might occur with lower lead levels. Venous blood lead levels were obtained at 6, 12, 18, 24, 36, 48 and 60 months of age in order to not only determine extent of systemic exposure (area under the blood lead curve or AUC), average peak lead levels, and estimated total lead burden over time. The relationship between IQ and blood lead concentration was estimated with the use of linear and nonlinear mixed effect models, with adjustment for maternal IQ, quality of home environment and other potential confounders. The study revealed that **IQ declined by 7.4 points** in a subset of 101 children whose maximal lead concentration remained below 10 μg/dl. This is higher than the 4.6 point decrease at higher lead levels. Based on this study the authors suggest that considerably more U.S. children are adversely affected by environmental lead exposure than previously estimated. However, the authors point out that while there is no effective treatment available for these lower lead levels, environmental protection is indicated.

Selevan SG *et al.* Blood lead concentration and delayed puberty in girls. NEJM 2003; 348: 1527–1536.

Previous studies of lead exposure showed that higher lead levels were associated with growth restrictions in both humans and laboratory animals. Studies in rats demonstrated that lead could affect the hypothalamic-pituitary-gonadal axis. The Third National Health and Nutrition Examination Survey (NHANESIII) assessed the relationship between **blood lead level** concentrations and **puberty status**. Non-institutionalised girls between the ages of 8 and 18 were studied. Race and ethnic background were either self-reported or proxy-reported. Measures of puberty included: pubic-hair stage for 1964 girls, breast development stage for 1986 girls, and age at menarche for 1796 girls. The girls' lead levels were also measured. As expected, the overall blood lead levels decreased with age. The mean lead levels were below 3 μg/dl for all groups. The analyses were adjusted for height, body mass index, family income (<$20,000 per year vs. > $20,000 per year), ever smoked 100 cigarettes, dietary intake of iron, vitamin C, and calcium. The study found that an increase from 1 μg/dl to 3 μg/dl was associated with statistically significant delays, ranging from two to six months, in breast and pubic hair development depending on the ethnic group.

McErlean M *et al.* Midazolam syrup as a premedication to reduce the discomfort associated with pediatric intravenous catheter insertion. J Pediatr 2003; 142: 429–430.

Oral midazolam has been used in children as pre-medication for anaesthesia and minor procedures such as endoscopy and laceration repair. However, it had not previously been studied in **line placement**. This study evaluated children aged nine months to six years who required intravenous line placement as part of their emergency department care. Subjects were randomly assigned to receive either oral midazolam syrup, 0.5 mg/kg (maximum 20 mg) or an equal volume of look alike, taste-alike placebo. The intravenous catheter was inserted twenty minutes after medication and a 100mm **visual analogue pain scale (VAS)** was used for evaluation. The two groups were stratified with respect to first intravenous line placement attempt, number of attempts, years of experience by the person placing the line, and the parent desire to use the medication again. Fifty one children were enrolled. The pain scores were lower in the midazolam group, but the results were not statistically significant (p=0.16). More parents would use the medication again versus placebo. While no patient showed an adverse effect to midazolam, the study was not designed to evaluate safety.

Editor's note: *Benzodiazepines are anxiolytic agents that produce sedation. In contrast, opiates are analgesics that have as a side effect the production of sedation. Absent in this study was the use of either a topical or systemic analgesic drug. The interpretation of the results is further complicated by their use of a scale designed to assess pain, not anxiolytic effect or sedation. Before valid conclusions from a pharmacodynamics study can be drawn, it is imperative that the appropriate outcome be assessed using measures that are sufficiently sensitive and specific to do so.*

Daniel KL *et al.* Sharing prescription medication among teenage girls: potential danger to unplanned/undiagnosed pregnancies. Pediatrics 2003; 111: 1167–1170.

Teenagers are known to **exchange medications**, a fact that is not always considered when medications are being prescribed. Consequently, **potentially teratogenic medications** may be exchanged between **teenage girls** without the knowledge of physicians or parents. In order to establish the incidence of sharing medication between teenage girls, 764 adolescents between the ages of 9 and 18 years were surveyed. 20.1% of girls reported ever borrowing or sharing medications from a peer and 14.5% reported sharing their prescriptions with someone else. The likelihood of sharing increased with age. This sharing and borrowing was not a "one time only" event as 7.3% of girls aged 15 to 18 reported sharing more than three times. Fully 10% of these girls reported that they shared because they desired "something stronger for pimples or oily skin." The authors conclude that potentially toxic, teratogenic medications (e.g., Accutane®) may be more frequently shared between adolescent girls who may not realise they are pregnant.

Hawton, K *et al.* Co-proxamol and suicide: a study of national mortality statistics and local non-fatal self poisonings. BMJ 2003; 326: 1006–1008.

Paracetamol/Propoxyphene combination products (coproxamol) are frequently utilised in **suicide attempts.** However, the exact frequency and lethality of coproxamol

had not been studied as thoroughly as paracetamol and tricyclic antidepressants. Therefore, researchers in England and Wales analysed national and local data on suicides and self poisonings from 1997 to 1999 for the incidence of suicides with coproxamol, tricyclic antidepressants or paracetamol. Of the 4162 drug related suicides, 18% involved coproxamol alone, 22% involved tricyclic antidepressants alone, and 9% paracetamol alone. **The highest proportion of suicide attempts with coproxamol occurred in the 10–24 year old age group**. The fatality odds with coproxamol were 2.3 times higher than that for tricyclics and 28.1 times that for paracetamol. The authors conclude that restricting the availability of coproxamol could have an important role in suicide prevention.

Editor's note: *Propoxyphene is an opioid which is structurally similar to pethidine. However, it has many side effects which make it uniquely more toxic than other opioids (e.g., dysrhythmias and seizures). Thus, a suicide attempt with a medication containing propoxyphene can be particularly lethal when compared to medications more commonly considered for suicide attempts.*

Shea KM *et al.* Pediatric exposure and potential toxicity of phthalate plasticizers. Pediatrics 2003; 111: 1467–1474.

Phthalates are plasticisers that are added to polyvinyl chloride (PVC) products to increase flexibility and durability. In order to provide an understanding of the current understanding of phthalates in paediatrics, the American Academy of Pediatrics (AAP) published a technical detailing the limited knowledge concerning phthalates. Phthalates are **found in a wide variety of products** including building materials, food packaging, clothing, toys, children's products, blood bags, and intravenous tubing / fluid bags. Phthalates are **known animal carcinogens** and can cause **fetal death, malformations**, **and reproductive toxicity in laboratory animals**. Two phthalates, diethylhexyl phthalate (DEHP) and diisononyl phthalate (DINP), have recently resulted in significant media attention due to their frequent **use in children's toys**. Exposure in humans is universal as substantial amounts (i.e., micrograms to milligrams per kg) of the substance are ingested by humans daily. However, no study has been performed to date to evaluate human toxicity from exposure to these compounds. The AAP calls for an improved understanding of the toxicokinetics of phthalates in order to further the understanding of their potential toxicity in potentially vulnerable subpopulations including pregnant and lactating women, premature infants and all children.

Editor's Note: *This report underscores how little is currently known about the toxicity of phthalates in all age groups, especially children. DEHP crosses the placenta and passes into breast milk. The US, Canada and the European Urion no longer allow the use of DEHP in nipples, teethers or toys designed for mouthing. However, DEHP remains ubiquitous as an environmental contaminant with a human toxicology profile that is ill-defined.*

Roy M *et al.* What are the adverse effects of ethanol used as an antidote in the treatment of suspected methanol poisoning in children? J Toxicol Clin Toxicol 2003; 41: 155–161.

Since the approval of **fomepizole** as a new antidote for **ethylene glycol poisonings** and more recently for **methanol poisonings**, **ethanol** has fallen from favour as the antidote of choice due to its purported side effects such as hypoglycemia, CNS depression, hypotension, and thrombophlebitis. However, the American Academy of Clinical Toxicology 2002 guidelines underscore that there is limited data on the complications of ethanol infusion, especially in children. Moreover, fomepizole is currently not approved for use in paediatrics. This retrospective chart review of the side effects over 20 years is the first to identify the **incidence of side effects of ethanol for the treatment of methanol poisoning in the pediatric population**. During the study period, 60 children (39 boys and 21 girls) received ethanol for suspected methanol poisoning. The median age of patients was 24 months (range 6 months to 18 years) with 45 patients 5 years of age or younger. **None of the 60 patients developed symptomatic hypoglycemia**. The only **adverse effects with ethanol included six episodes of drowsiness and one episode of hypotension**. The authors suggest that ethanol is a safe and effective antidote for children in a tertiary care hospital setting for the treatment of methanol poisoning.

Editor's note: *Fomepizole has been used with remarkable success and safety in many children and from a pharmacokinetic perspective, easier to dose than ethanol. The fact that fomepizole is not approved (i.e. labelled) for paediatric use should not adversely influence treatment decisions when it is determined by the physician to represent the best option for treating methanol poisoning in a child.*

Diary

9th Congress of the European Society for Developmental, Perinatal and Paediatric Pharmacology

Marburg, Germany – June 16th–20th 2004

The 9th Congress of the ESDP will cover the areas of pharmacogenomics, pharmacovigilance, PK-PD modelling, development of orphan drugs, free communications as well as scientific sessions on prostanoids and channelopathies in the kidney.

For further details please contact
esdp@med.uni-marburg.de

2nd International Workshop on Paediatric and Perinatal Drug Therapy

London, Ontario, Canada – October 15th–16th 2004

Following the success of the 1st international workshop, a 2nd international workshop is planned covering the area of paediatric clinical trials. The workshop will include lectures and interactive workshops from key investigators and free communications by young investigators. It will be organised by PPDT and the ACRP.

For further details please contact Eileen Moynihan; Eileenm@acrpnet.org