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Trends in Paediatric Pharmacology and Toxicology

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Avci Z *et al.* Nephrolithiasis associated with ceftriaxone therapy: a prospective study in 51 children. Arch Dis Child 2004; 89: 1069–1072.

A well known side effect of ceftriaxone is its ability to bind to calcium ions causing biliary sludging or biliary pseudolithiasis. More recently, there have been case reports implicating ceftriaxone as a causative agent of nephrolithiasis. In a study designed to assess the incidence of this adverse effect, 51 children with normal renal function and calcium levels were studied. Twenty four children with severe infection received 100 mg/kg/day ceftriaxone while 27 children had milder infection and received 50 mg/kg/day IM. Duration of treatment ranged from 5 to 10 days. Post-treatment ultrasound revealed renal stones in 4 of 51 children (7.8%), with two receiving the lower dose and two receiving the higher dose. Higher doses were associated with the development of larger stones. The stones measured ≤ 2 mm in diameter and were still apparent 7 months after treatment, except in one case where the stones disappeared spontaneously. While stone development was apparently benign, there may be increased risk for larger stones and renal damage with high-dose, long-term ceftriaxone therapy. The authors recommend these patients receive follow-up renal function testing and ultrasounds.

1Polos P *et al.* Montelukast vs fluticasone in patients aged 6 to 14 with mild persistent asthma: the MOSIAC study. Eur Respir J Suppl 2004; 24: 377.

[2]Henschen M *et al.* Long-term efficacy of 1 year anti-inflammatory treatment in paediatric patients with mild persistent asthma. Eur Respir J Suppl 2004; 24: 379.

[3]Bisgaard H *et al.* Efficacy of motelukast in patients aged 2 to 5 years with mild asthma. Eur Respir J Suppl 2004; 24: 377.

[4]Lotufo JPB *et al.* Montelukast vs. beclomethasone for the clinical control of moderate persistent asthma in children. Eur Respir J Suppl 2004; 24: 377.

Inhaled corticosteroids are commonly used as first-line therapy in children with persistent asthma. However, due to their potential for causing adrenal suppression and growth retardation, other therapies have been investigated. Recent studies presented at the 14th Annual Congress of the European Respiratory Society suggest that oral montelukast may provide an alternative to inhaled corticosteroids in children with mild persistent asthma.

The MOSAIC study, a large (n=495) randomised, double blinded 12 month study, compared twice daily fluticasone (100 µg) to once daily oral montelukast (5 mg) in children 6 to 14 years of age. The main outcome variable was the number of rescue-free days. Asthma control was assessed using a questionnaire, the Paediatric Asthma Therapy Assessment Questionaire and changes in the patient's baseline FEV_1. According to their reported results, both therapies significantly decreased in β-agonist use while fluticasone was associated with a 0.41 cm mean difference in height[1].

In a separate study, montelukast (4 mg tablets) was shown to decrease daytime asthma symptom scores in patients 2 to 5 years of age[3]. The long-term anti-inflammatory effects of montelukast (5 mg) and fluticasone (100 µg) were compared in another study in children 6 to 14 years of age over a 12 month period[2]. The outcome variables included lung function, exhaled NO before and after therapy, ECP (eosinophil cationic protein) in sputum and serum, and the eosinophil cell count. Both treatments showed similar decreases in FEV_1, the number of symptomatic days per month, ECP and eosinophil counts. There was no change in exhaled NO throughout the study. The differences between the two treatments were not statistically significant. When comparisons were made between beclomethasone and montelukast, another study found montelukast showed similar efficacy to beclomethasone in children with moderate persistent asthma[4].

Butler K *et al.* Adherence of pediatric asthma patients with oral corticosteroids prescriptions following pediatric emergency department visit or hospitalisation. Pediatr Emerg Care 2004; 2: 730–735.

Children presenting to the emergency room (ER) for asthma exacerbations account for a high number of patient ER visits per year. The prompt use of oral corticosteroids during an acute episode is used to not only decrease symptoms and hospitalisation but also, to decrease the relapse rate. Guidelines issued by the National Institutes of Health recommend that children with an asthma exacerbation have a three to ten day course of oral corticosteroids therapy after discharge from the ER. Successful treatment of asthma symptoms with corticosteroids often depends upon family adherence to the prescribed regimen. A recent study using a telephone administered interview 7–9 days after ER discharge found that 1% of caregivers do not fill the prescription. Only 64% of caregivers adhered to the full course of corticosteroids with male children being more likely than females to receive an adequate course of treatment. Barriers to treatment included: side effects (60%), trouble giving the prescription to the child (26%), lack of understanding how the medication worked (23%), and lack of family support (17.6%). The authors concluded that the length of therapy and caregiver perception of perceived side effects should be considered when prescribing oral corticosteroid therapy.

Konofal E *et al*. Iron deficiency in children with attention deficit/hyperactivity disorder. Arch Pediatr Adoles Med 2004; 158: 1113–1115.

Previous reports have suggested iron deficiency is a potential cause of poor cognitive function and learning disabilities. As iron is a coenzyme for dopamine synthesis, decreased iron stores can influence dopamine-dependent functions. Iron is bound to ferritin in the brain and low ferritin levels in childhood have been shown to affect the development of the CNS. Symptoms of ADHD such as altered executive functions and inattention are possibly modulated by the dopaminergic mesocortical pathways. Affected patients have alterations in their dopamine receptors which suggest that symptoms of ADHD may be caused by dopamine dysfunction. A recent study evaluated 53 children (4–14 years of age) and 27 age and sex-matched controls for a relationship between iron deficiency and ADHD. Mean serum ferritin levels were lower in children with ADHD (23 ± 13 ng/ml) as compared to controls (44 ± 22 ng/ml; p<.001). In addition, 42 of the 53 children in the ADHD group had abnormally low serum iron levels (<30 ng/ml) as compared with only 5 of 27 controls. Researchers also evaluated severity of disease using Conners' Parent Rating Scale and found that serum ferritin levels correlated with ADHD symptoms and severity in the ADHD group. Results of this study suggest that decreased iron stores may contribute to ADHD symptoms and that iron supplementation should be considered for treatment of children with ADHD and iron deficiency.

Fleece D *et al*. Griseofulvin versus terbinafine in the treatment of tinea capitis: A meta-analysis of randomised clinical trials. Pediatrics 2004: 114; 1312–1315.

The current standard of the treatment of tinea capitis is griseofulvin given once daily for 6 to 8 weeks. A recent meta-analysis of randomised clinical trials comparing griseofulvin to terbinafine suggests that terbinafine is at least equally as effective as griseofulvin in the treatment of tinea capitis due to *Trichophyton* infections. The analysis was performed on 6 of 43 studies that were included if comparisons of terbinafine and griseofulvin were conducted in a randomised clinical trial, an infecting agent was identified and reported post-therapy cultures were reported as an outcome measure. The griseofulvin treatment course in these studies had to be at least 6 weeks in duration. Cure was defined as a negative scalp fungal culture with either no symptoms ("complete cure") or minimal symptoms ("mycologic cure"). Two of the included studies found statistically significant differences in cure rates. One study showed griseofulvin to have superior cure rates, however 100% of the reported pathogens in this study were *Microsporum* species. The other study found that terbinafine was superior at the 12 week follow up but not at 8 weeks. The pathogen distribution for this study was 74% *Trichophyton* and 26% *Microsporum*. When the meta-analysis included all 6 studies, no statistically significant differences were observed between the two medications. However, if the study containing 100% *Microsporum* species was removed, odds ratios favoured shorter courses of terbinafine (OR 0.65; 95%CI: 0.42-1.01; *P*=0.54). The authors conclude that terbinafine may be an equally effective option for tinea capitis. However, no liquid preparation is currently available and treatment of tinea capitis is not an FDA approved indication for terbinafine use. The potential benefits of terbinafine include better compliance due to shorter courses of therapy and cost savings.

Gasche Y *et al*. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. N Engl J Med 2004; 351: 2827–2831.

A recent report provides a very interesting example of the importance of considering pharmacogenetics and drug metabolism when evaluating a complex drug-drug interaction. related to metabolism. A patient with a history of chronic lymphocytic leukaemia presented with signs and symptoms consistent with bilateral pneumonia. He was started on ceftriaxone, clarithromycin, and voriconazole. Additionally, he was given codeine, 25 mg three times a day for cough. On hospital day 4, the patient became unresponsive, GCS 6, pO_2 of 56 mm Hg and pCO_2 of 80 mm Hg. His pupils were miotic and creatinine elevated at 2.1 mg/dl. There was marked improvement in his level of consciousness and his respiratory failure resolved after naloxone administration. Codeine is a substrate for both CYP 3A4 (major pathway) and CYP 2D6 (minor pathway responsible for biotransformation of codeine to morphine). CYP2D6 genotyping revealed that the patient had a phenotype consistent with ultra-rapid metabolism (i.e. enhanced conversion to morphine). Thus, co-administration of clarithromycin and voriconazole resulted in inhibition of CYP3A4 and thereby, removed the major route for codeine biotransformation to inactive metabolites. This left enhanced CYP2D6 activity as the predominant route for codeine metabolism which in this instance, resulted in its metabolic activation (i.e. conversion to morphine). When coupled with a significant reduction in renal function, the end result that was produced was opiate intoxication (confirmed by naloxone response). This case underscores the complexity of predicting drug-drug interactions when polymorphically expressed enzymes are involved. It also supports the potential utility of genotype and phenotype determination to assist in the assessment of these interactions and ultimately, in drug selection.

Cheuk DKL *et al*. A meta-analysis on intravenous magnesium sulfate for treating acute asthma. Arch Dis Child 2005; 90: 74–77.

Some children presenting with moderate to severe acute exacerbations of asthma do not respond adequately to inhaled ß-agonists and corticosteroids. While IV magnesium sulfate has been shown to be effective in adults with refractory asthma symptoms, its utility in paediatrics remains unproven. A recent meta-analysis evaluated the efficacy of IV magnesium sulfate for refractory status asthmaticus in children. Five randomised, placebo controlled trials involving 182 children were identified. Studies compared IV magnesium to placebo with co-therapies of inhaled ß-agonists and systemic steroids administered in an emergency department. This analysis showed that IV magnesium significantly reduced the need for hospitalisation (primary outcome; OR 0.290, 95% CI 0.143 to 0.589). The authors suggest that magnesium sulfate be considered as a first line treatment of acute asthma exacerbation in paediatric patients.

[1]Abu-Kishk I *et al*. Neuroleptic malignant syndrome in a child treated with an atypical antipsychotic. J Toxicol Clin Toxicol 2004; 42: 921–925.

[2]Silva RR *et al*. Neuroleptic malignant syndrome in children and adolescents. J Am Acad Child Adolsc Psychiatry 1999; 38: 187–194.

The Neuroleptic Malignant Syndrome (NMS) is an uncommon but potentially fatal adverse reaction of neuroleptic drugs with antidopaminergic activity. It is characterised by movement disorder, altered mental status and autonomic instability. In a report from Israel[1], an 11 year old male developed signs and symptoms consistent with NMS on two separate occasions after receiving a single dose of two different atypical antipsychotic agents (clotiapine and olanzapine). There are only rare case reports of NMS in children treated with the newer group of atypical antipsychotics. NMS has been seen with all neuroleptics in current use including phenothiazines, butyrophenones, thioxanthenes, benzamides, and novel antipsychotic agents. The incidence in adults ranges from 0.02 to 3.23% but is unknown for children and adolescents. A retrospective review of NMS in children found 77 cases during 32 years, with the syndrome persisting from 1 to 119 days and associated with 9% fatalities and 20% serious sequelae in survivors[2].

The introduction of atypical antipsychotic drugs was hoped to decrease the incidence of extrapyramidal signs as well as NMS. The potential of any drug inducing NMS is related to the anti-dopaminergic activity in the CNS. This action causes muscle rigidity, heat production and altered thermoregulation in the hypothalamus. NMS occurs twice as often in males and in all age groups with a reported mean age of 40 years. The onset ranges from 1 to 44 days (mean 10) following institution of therapy. Recovery usually occurs over 2–3 weeks. The mortality rate is estimated to be 5–12%. NMS is a diagnosis of exclusion; an elevated CPK is considered to be a major criteria and occurs in about 97% of patients. When NMS is suspected, treatment consists of immmediate cessation of the offending drug, supportive measures such as rehydration, respiratory support, cooling and benzodiazepines

for muscle rigidity. Adjunctive therapies include dantrolene (a muscle relaxant which inhibits calcium release), bromocriptine (a dopamine agonist) and other less studied therapies (e.g. amantidine, levodopa/carbidopa, electro-convulsive therapy).

Hsieh K *et al.* Treatment of acute Kawasaki disease: aspirin's role in the febrile stage revisited. Pediatrics 2004; 114: 689–693.

The most significant complications of Kawasaki disease (KD) are coronary arteritis and aneurysm formation. While intravenous immunoglobulin (IVIG) has been shown to reduce the duration of fever and decrease the incidence of coronary arteritis/aneurysms, the role of aspirin during the acute phase of the illness is not clear. A recent investigation evaluated the outcomes of patients who did not receive aspirin therapy during the acute phase of KD and compared them to historical controls. This study was a retrospective review of 162 children who were diagnosed with acute KD. All patients received 2 g/kg of IVIG as a single dose with paracetamol given for fever ≥ 38ºC. Aspirin, 3–5 mg/kg/day, was prescribed only after fever subsided. If fever persisted 3 days after the first dose of IVIG a second dose was given. Echocardiography was performed at diagnosis and 2, 4 and 8 weeks after treatment. Ninety-four percent (n = 153) of the patients were afebrile within 3 days after IVIG therapy, with 128 of these patients (83.7%) afebrile in the first 24 hours. Of the nine patients who failed initial therapy after the first dose of IVIG, 6 (66.7%) became afebrile after a second dose of IVIG without aspirin therapy. There was no significant difference in the response to IVIG therapy without aspirin between those who started therapy prior to day 5 of the illness and those who started after day 5 (P=0.66). These response rates to IVIG therapy were similar to those reported in studies where aspirin was given during the acute phase of the illness. The authors conclude that treatment without aspirin during the acute phase of KD has no effect on the response rate of IVIG therapy, duration of fever, or the incidence of coronary artery abnormalities.

[1]Weizman Z *et al.* Effect of a probiotic infant formula on infections in child care centers: comparison of two probiotic agents. Pediatrics 2005; 115: 5–9.

[2]Lin HC *et al.* Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. Pediatrics 2005; 115: 1–4.

[3]Rosenfeldt V *et al.* Effect of probiotics on gastrointestinal symptoms and small intestinal permeability in children with atopic dermatitis. J Pediatr 2004; 145: 612–616.

Probiotics are nonpathogenic bacteria that can colonise the intestine, modify the balance of intestinal microflora and may improve natural immunity. A recent double-blinded, placebo-controlled, randomised 12 week trial[1] attempted to study if probiotics could aid in the prevention of common infectious respiratory and gastrointestinal illnesses in the day care centre setting. The study enrolled infants 4 to 10 months of age who were randomly assigned to receive formula supplemented with either *Bifidobacterium lactis* or *Lactobacillus reuteri*, or formula without probiotic supplementation. The main outcome measures included number of days and episodes with fever (>38ºC) and number of days and episodes with diarrhoea or respiratory illness. A total of 201 infants were enrolled, 73 received *B. lactis* and 68 received *L. reuteri*. The study found that controls (n=60) had more fever and diarrhoea episodes compared to either of the two probiotic groups (*B. lactis* or *L. reuter*; CI of 0.41 vs 0.27 vs 0.11, respectively). Diarrhoea episodes were of longer duration in the control group. Interestingly, the *L. reuteri* group when compared to the controls or those receiving *B. lactis* had a significant decrease in the number of days with fever (P=0.001), clinic visits (P=0.002), child care absences (P=0.015), and antibiotic prescriptions (P=0.37). The rate and duration of respiratory illnesses did not differ significantly between the three groups. The investigators concluded that infants fed with formula supplemented with either of the probiotics had fewer and shorter episodes of diarrhoea with the effects being more prominent with L *reuteri*.

A second study[2] investigated the effects of probiotics on innate immunity in the neonatal intestine by examining their impact on the incidence and the severity of necrotising enterocolitis (NEC) in very low birth weight infants (VLBW; less than 1500 grams). This prospective randomised study fed their experimental group a product (Infloran®) containing a mixture of *Lactobacillus acidophilus* and *Bifidobacterium infantis* with breast milk twice daily until discharge. The control group was fed breastmilk alone. The primary outcomes examined were death or NEC ≥ stage 2. The incidence of death or NEC was significantly lower in the study group (9/180 vs 24/187; P=0.009). There were 6 cases of severe NEC (stage 3) in the control group and none in the study group. The incidence of NEC (> stage 2) or sepsis was also lower in the probiotic groups (24/180 vs 46/187; P=0.03). No cultures from probiotic-treated patients grew either *Lactobacillus* or *Bifidobacterium* species. Based on their results, the authors advocate probiotic treatment with a combination of *L. acidophilus* and *B. infantis* to reduce the incidence and severity of NEC in VLBW infants.

A third study[3] investigated the influence of probiotics on small intestine permeability using a lactulose-mannitol test. This test evaluates the urinary excretion of a large molecule (lactulose) compared to a small molecule (mannitol). Urinary excretion ratios correspond to either an intact mucosal barrier (i.e. a smaller ratio) or alternatively, one where absorptive surface area is decreased (i.e. larger ratio). This double-blinded, placebo-controlled, cross-over study used *Lactobacillus rhamnosus* and *L reuteri* as probiotics for 6 weeks in 41 children (1 – 13 years of age) with moderate and severe atopic dermatitis. The main outcome measures were the urinary lactulose to mannitol ratio and the frequency of gastrointestinal symptoms assessed by a questionnaire. The investigators found that *Lactobacillus* supplementation decreased the frequency of GI symptoms (39% vs 10%). They also found that after probiotic therapy, the lactulose to mannitol ratio was lower than after placebo (0.073 vs 0.110; P=0.001). These data suggest that probiotics may decrease gastrointestinal symptoms in children with atopic dermatitis by stabilising the intestinal barrier.

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