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Trends in Paediatric Pharmacology and Toxicology

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Sheu B, et al. Pretreatment with *Lactobacillus*- and *Bifidobacterium*-containing yogurt can improve the efficacy of quadruple therapy in eradicating residual *Helicobacter pylori* infection after failed triple therapy. Am J Clin Nutr 2006; 83: 864–869.

The recommended first line regimen to treat *Helicobacter pylori* is a triple therapy containing a proton pump inhibitor and two antibiotics. While this treatment is effective, it still has a 10–23% failure rate. Quadruple therapy is often used in those patients who fail triple therapy. Previous studies have found that *Lactobacillus acidophilus*- and *Bifidobacterium*-containing yogurt (AB-yogurt) suppress the growth of *H. pylori*. In this trial, 138 subjects with known *H. pylori* infections who previously failed triple therapy were randomly assigned to quadruple rescue therapy with or without pretreatment with AB yogurt. Those who were assigned to the AB yogurt pretreatment group received AB yogurt twice a day for 4 weeks prior to starting quadruple therapy. Patients enrolled in this study were also enrolled in a culture study of H. pylori to assess resistance patterns. Therefore, this study also evaluated whether quadruple therapy eradication efficacy was improved in those patients with metronidazole-resistant *H. pylori* by pretreatment with AB yogurt. The AB yogurt group had 85.5% eradication rate while the non-yogurt group had 71.1% eradication rate according to an intention-to-treat analysis ($P < 0.05$). Patients with metronidazole-resistant *H. pylori* had a lower per protocol eradication rate with quadruple therapy than patients with metronidazole-sensitive *H. pylori* $P < 0.01$). The study concluded that four weeks pretreatment with AB yogurt decreases the bacterial load of *H. pylori* in patients with both antibiotic-sensitive and -resistant *H.pylori* and improves the eradication rates of quadruple therapy following failed triple therapy.

Passeron T, et al. Prebiotics and synbiotics: two promising approaches for the treatment of atopic dermatitis in children above 2 years. Allergy 2006; 61: 431–437.

Appropriate use of **prebiotics** and **probiotics** may improve symptoms of **atopic dermatitis** (AD) in children 2 years of age and older. Probiotics are viable micro-organisms that exhibit a beneficial effect on the health of the host. Prebiotics are substances that benefit the host by stimulating the growth or activity of bacterial strains already a part of the gut flora. Synbiotics are the combination of prebiotics and probiotics. Patients with AD are believed to have an imbalance in the T-helper lymphocyte ratio (Th1/Th2). Probiotics such as *Lactobacillus rhamnosus* appear to help restore the balance of T-helper lymphocyte ratio to normal. A recent report investigated whether prebiotic adjuncts to probiotic strains increase viability of the probiotic thereby improving the efficiency of the probiotic in decreasing the manifestations of AD. Forty-eight patients (mean age 5.82 years) were randomised to receive treatment with a synbiotic or prebiotic only. Patients continued on their usual topical treatments. Both groups were found to have statistically significant improvement in their AD symptoms after 3 months using the SCORing Atopic Dermatitis (SCORAD) score. However, there was no difference between the two treatment groups. Similarly, there was a significant decrease in the overall use of steroid or tacrolimus ointments in both groups at the end of the 3 month study compared to base line. Again, there were no statistically significant differences between the two groups in the total use of topical ointments. The authors concluded that synbiotics and prebiotics alone reduce the manifestations of AD in children greater than 2 years of age.

Gelfand EW, et al. Once-daily ciclesonide in children: efficacy and safety in asthma. J Pediatr 2006; 148: 377–383.

Inhaled corticosteroids (ICS) are now the mainstay of treatment for persistent childhood asthma. Concern for adverse systemic effects that include suppression of the hypothalamic–pituitary–adrenal (HPA) axis, growth impairment, and oral candidiasis have produced hesitance among paediatricians to prescribe these agents. **Ciclesonide** is a novel ICS with low bioavailability, rapid clearance, and high degree of protein binding that may have an advantage over existing ICS for the treatment of asthma. In a recent randomised, double-blind, placebo-controlled study, the efficacy and safety of ciclesonide was studied in 1031, children aged 4 to 11 yr, with persistent asthma of all severities. Subjects received placebo or doses of 40, 80, or 160 microg daily in a single dose administered without a spacer for 12 weeks. Improvement in FEV_1 occurred in all ciclesonide groups in a dose-ordered fashion. Significantly greater improvement occurred in the two higher dose groups. Asthma symptom scores and bronchodilator use was also significantly improved in subjects receiving the two higher doses of ciclesonide. Additionally, the percentage of patients who discontinued the study due to lack of efficacy was lower in ciclesonide-treated subjects. Discontinuation rates were comparable in all groups, with worsening of asthma symptoms cited as the most common reason. Three patients had positive cultures for oral candidiasis. HPA axis function was not different from baseline in any treatment group. The authors suggest that ciclesonide represents another ICS option for the treatment of asthma and has a side-effect profile similar to other agents in this class.

Johnston SL, et al. The effect of telithromycin in acute exacerbations of asthma. N Engl J Med 2006; 354: 1589–1600.

Ketolides are a new class of antibiotics structurally related to macrolides with activity against *Mycoplasma* and *Chlamydia* species. They have also been shown to have immunomodulatory effects *in vitro* and *in vivo*. Based on these attributes, a recent study investigated whether **telithromycin** would improve **asthma symptoms**. A total of 278 adults with asthma were enrolled in this randomised, double-blind, placebo-controlled study. Within 24 hours of an acute asthma exacerbation, patients were randomly assigned to receive a

10 day course of telithromycin (800 mg/day) or placebo in addition to usual care. During the treatment period, patients in the two groups were also matched with respect to the percentage receiving oral or inhaled corticosteroids as well as the use of short-acting β-agonists. Mean scores on a test of asthma symptoms was significantly reduced in the telithromycin-treated group relative to placebo controls (mean difference: –0.3; 95% CI –0.50–0–1.0; $P = 0.004$). The authors found that the drug had no effect on measure of morning peak expiratory flow. Nausea, the most common adverse effect, was more common in the treatment group. A total of 61% of patients met at least one criterion for infection with chlamydia pneumonia, mycoplasma pneumonia, or both. However, subgroup analysis indicated no relationship between bacteriologic status and the response to asthma treatment. The authors posit that telithromycin may be useful for the treatment of asthma due to an as yet unidentified immunomodulatory mechanism that is independent of its bactericidal effects.

Baquero H, et al. Oral sildenafil in infants with persistent pulmonary hypertension of the newborn: a pilot randomised blinded study. Pediatrics 2006; 117: 1077–1083.

Sildenafil has been used to treat pulmonary hypertension in adults with beneficial results. In a proof-of-concept, randomised, blinded study in neonates, the use of sildenafil in infants ≥ 35.5 weeks gestational age and < 3 days postnatal age with **severe persistent pulmonary hypertension of the newborn** (PPHN) was evaluated for ease of administration and its effect on oxygenation. Thirteen patients (n=7 in the treatment group) were enrolled in this study. The dose of sildenafil used was 1–2 mg/kg/dose given every 6 hours. The placebo was Orabase®, the diluent used for the sildenafil formulation. Clinical management protocols used in the NICU by attending physicians caring for infants with PPHN were not modified for those infants in the study. The mean baseline oxygenation index (OI) before treatment was 56 in the sildenafil group and 46 in the placebo group. The PaO_2 at entry was 34.2 ± 12.5 and 42.7 ± 11.3 mm Hg in the treatment versus placebo groups, respectively. Oral sildenafil produced significant changes from baseline in OI compared to placebo at 12, 24, and 36 hours after the first study dose. There were significant differences in PaO_2 between the groups which became significant over time after 4 doses or 36 hours after study entry. An average of 6-7 doses of sildenafil was required to obtain on OI of < 20 (a ≥ 50% decrease in OI). There were no noticeable effects on BP during the study period. No significant changes in morbidity or mortality can be extrapolated at this time, although survival for the treatment group was 6/7 and the placebo group was 1/6. The results of this study, although limited in size, show sildenafil as being a promising drug for the treatment of PPHN.

FDA

The US Food and Drug Administration (FDA) notified healthcare professionals and patients that cases of breathing problems, some causing death, have been reported to the FDA when promethazine was used in children less than 2 years old. Medications containing promethazine should not be used for children less than two years of age because of the potential for fatal respiratory depression. The FDA has received postmarketing reports of serious adverse events, including seven deaths and 22 cases of respiratory depression, that were associated with use of promethazine in children younger than 2 years. This includes the drug in any form: syrups, suppositories, tablets, or injectables. Caution should also be exercised when administering promethazine HCl in any form to paediatric patients two years of age and older. The labelling on all products, brand name and generic, has been changed to reflect these strengthened warnings. One manufacturer of suppositories and tablets has notified healthcare professionals of the changed label. The FDA is issuing this safety alert to make sure that healthcare professionals, other caregivers, and patients realise that the warnings apply to promethazine syrups as well.

Readers may be interested to look at a paper published more than 20 years ago which highlighted the risk of sleep apnoea in infants following the administration of promethazine.

Kahn A et al. Phenothiazine-induced sleep apnoeas in normal infants. Pediatrics 1985; 75: 844–847

[1]Bisgaard H, et al. Intermittent inhaled corticosteroids in infants with episodic wheezing. N Engl J Med 2006; 354: 1998–2005.

[2]Guilbert TW, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. N Engl J Med 2006; 354: 1985–1997.

While there is considerable evidence that indicates that daily therapy with inhaled corticosteroids (ICS) is effective in reducing symptoms in high-risk children with frequent wheezing, a long term benefit in reducing the progression of disease has not been established. Two recent reports test the hypothesis that the failure of ICS to prevent disease progression is due to starting the treatment too late in life. In the first study[1], 411 high risk one month old infants were randomly assigned to receive two week courses of budesonide (400 microg/day) or placebo after having symptoms of wheezing for three days. Children were followed for three years. The results showed no difference in the number of symptom-free days or the use of rescue medications. The incidence of symptoms was similar between both groups and independent of respiratory viral status. Moreover, there was also no difference in the number of patients withdrawn from the study due to persistent wheezing (Hazard ratio: 1.22; 95%CI 0.71 – 2.13). Based on their results, the authors conclude that not only does ICS provide no short-term relief of symptoms in children 1 month to 3 years of age, but also, has no effect on the long-term progression from episodic to persistent wheezing.

A separate study enrolled children 2–3 years of age who were at high risk for asthma[2]. They were randomly assigned to receive either ICS (fluticasone proprionate; 88 microg, twice a day) or placebo for two years after which treatment was stopped. Children were then followed for an additional year. During the two year treatment period, there was a significantly greater proportion of episode-free days in the ICS-treated group (93.2%; 95%CI 91.1 – 94.9) compared to the placebo group (88.4%; 95%CI 84.9 – 91.2) ($P < 0.006$). Children in the ICS group also had a lower rate of exacerbations that required a course of systemic corticosteroids. In contrast, there was no difference in the proportion of episode-free days between study groups during the observation year after discontinuation of ICS. Height was significantly less in the ICS treatment group with a 1.1 cm difference observed at the end of the two year treatment period (12.6±1.9 cm vs 13.7±1.9 cm; $P < 0.001$) and an 0.7 cm difference (19.2±2.2 cm vs 19.9±2.2 cm; $P < 0.008$) observed after the third observation year. Thus, clinical improvement was observed while children were being treated with ICS, but this improvement was not sustained after treatment was discontinued. In contrast to previous reports in older children, ICS use was associated with reduced height in this age group. Collectively, results from these two studies suggest that while ICS may help control active symptoms in older children, the natural course of asthma is not modified by their use.

[1]Thiboutot DM, et al. Adapalene gel, 0.1%, as maintenance therapy for acne vulgaris. Arch Dermatol 2006; 142: 597–602.

[2]Leyden J, et al. Comparison of tazarotene and minocycline maintenance therapies in acne vulgaris. Arch Dermatol 2006; 142: 605–612.

The use of topical retinoids may reduce the need for systemic antibiotics in the treatment of moderate to severe acne and decrease the prevalence of antibiotic-resistant strains of *Propionibacterium acnes*. Two recent reports assess the efficacy of topical retinoid treatment for maintenance therapy for acne. In one study[1], 253 patients (aged 12–30 yr) with severe acne were enrolled who had a positive response in a previous 12 week study comparing treatment with adapalene and/or doxcycyline (100 mg once a day). Patients were randomly assigned to receive subsequent maintenance therapy with either adapalene gel (0.1%) or gel vehicle for an additional 16 weeks. Patients receiving adapalene treatment had a significantly larger maintenance rate (75% vs 54%; $P < 0.001$), defined

as a percentage of the increase in number of lesions after the 16 week maintenance period divided by the number of lesions lost during the previous combination study. Adverse events including erythema, dryness, scaling, and stinging/burning were not different between groups. The other study[2] employed a similar design that involved an initial 12 week treatment phase where patients received both tazarotene gel (0.1%) and minocycline hydrochloride (100 mg twice a day). Those patients showing a 75% or greater global improvement at the end of the open-label period were randomly assigned to groups receiving an additional 12 weeks of maintenance therapy with either tazarotene gel plus placebo capsules, vehicle gel plus minocylcine capsules, or tazarotene gel plus minocycline capsules. In the sample population of 189 individuals, no significant differences in non-inflammatory or inflammatory lesions were found between any of the treatment groups after 16 weeks. By 24 weeks, greater than 80% of patients in each group maintained 50% or greater global improvement, whereas over 50% of patients maintained a global improvement of 75% or greater. Based on their findings of non-inferiority, these authors suggest that tezarotene monotherapy is an effective maintenance therapy for moderate to severe acne. Both studies are limited by their assessment of successful maintenance therapy only in initial responders. However, they do provide evidence that the use of topical retinoids may be useful to help minimise antibiotic exposure.

[1]Schmidt, B. et al. Caffeine therapy for apnea of prematurity. N Engl J Med 2006; 354: 2112–2121.

[2]Bancalari, E. Caffeine for apnea of prematurity. N Engl J Med 2006; 354: 2179–2181.

Methylxanthines are typically prescribed to preterm infants for the treatment of apnoea of prematurity. However, data on additional short- and long-term outcomes are lacking. The short-term outcomes associated with caffeine administration were addressed in a recent randomised placebo-controlled trial. The results of the primary outcome, a composite of death, cerebral palsy, cognitive delay, deafness, or blindness, are not expected to be complete until December 2006. Premature infants (n = 2006; 500 – 1250 g) were randomly assigned to receive caffeine or placebo for the treatment of apnoea and bradycardia. 36% of infants in the caffeine group who were still alive at 36 weeks postmenstrual age were diagnosed with bronchopulmonary dysplasia (BPD) while 47% of infants in the placebo group were diagnosed with BPD (adjusted odds ratio, 0.63; 95% CI 0.52–0.76; $P < 0.0001$). Additionally, positive airway pressure was discontinued significantly sooner in caffeine-treated infants. The rates of death before discharge home, ultrasonographic signs of brain injury, and necrotising enterocolitis did not differ significantly between the two groups. The weight gain of patients in the caffeine was significantly less than the weight gain in the placebo group during the first 3 weeks of treatment. Interestingly, patients in the placebo group had a higher incidence of patent ductus arteriosus in a *post hoc* analysis. The authors suggest that additional studies are needed to clarify the effects of caffeine on ductal closure. With the results of the primary outcomes still pending, final decisions related to the short- versus long-term benefits of caffeine therapy should still be interpreted with caution.

Miller SP, et.al. Prolonged indomethacin exposure is associated with decreased white matter injury detected with magnetic resonance imaging in premature newborns at 24 to 28 weeks gestation at birth. Pediatr 2006; 117: 1626–1631.

Non-cystic white matter injury on magnetic resonance imaging (MRI) in premature newborns is associated with abnormalities of early motor and cognitive function. A recent report tested the hypothesis that prolonged treatment of premature newborns with indomethacin may decrease the occurrence of white matter injury. In this prospective cohort study, 57 premature infants (GA = 24 – 27 weeks) were studied with MRI at a median age of 31.1 weeks postmenstrual age. Moderate to severe white matter injury was detected in 12 (21%) of 53 newborns, minimal white matter injury was detected in 13 (25%), and no white matter injury in 28 (53%). Using a univariant analysis, the presence of haemodynamically significant PDA and prolonged indomethacin exposure was associated with a decreased incidence of moderate to severe white matter injury. Since a haemodynamically significant PDA was strongly associated with prolonged indomethacin exposure (P = 0.0001), a separate multivariate model was employed which showed that indomethacin exposure was independently associated with reduced risk of white matter injury (Odds Ratio [OR] 0.088; 95% CI 0.002 – 0.99; P = 0.049). When the analysis was adjusted for other possible confounding clinical variables (e.g. gestational age at birth, prenatal betamethasone, systemic infection, days of mechanical ventilation) there was an even stronger association between prolonged indomethacin and decrease in white matter injury (OR 0.037; 95% CI 0.004 – 0.69; P = 0.02). The authors suggest that the effects of indomethacin may be mediated by their ability to alter cerebral haemodynamics. They expressly do not suggest that their results should be used to guide clinical practice, but rather propose that randomised trials of prolonged indomethacin treatment be conducted to determine whether it can interrupt the inflammatory process and decrease white matter injury and subsequent neurodevelopmental abnormalities.

[1]Bellinger DC, et al. Neuropsychological and renal effects of dental amalgam in children: a randomized clinical trial. J Am Med Assoc 2006; 295: 1775–1783.

[2]DeRouen TA, et al. Neurobehavioral effects of dental amalgam in children: a randomized clinical trial. J Am Med Assoc 2006; 295: 1784–1792.

Adverse neuropsychological and renal effects of mercury vapour released from dental amalgams were investigated in two recent randomised clinical trials. In one study, 534 children 6–10 years of age requiring dental restoration of caries, were randomly assigned to receive using either amalgam or resin composite[1]. All the children studied had no prior amalgam restorations and required at least two fillings in permanent teeth. Although there was a significantly higher mean urinary mercury level after 5 years in the amalgam-treated group (0.9 microg/g vs 0.6 microg/g; $P < 0.001$), no significant difference in full-scale IQ, General memory index, or Visuomotor composite was observed. Additionally, albumin levels at five years did not differ between groups. A similar study conducted in Portugal reported comparable results[2]. In this study, 507 children aged 8–10 yr were followed over 7 years. Again, creatinine-adjusted urinary mercury concentrations were higher in the amalgam-treated group. The mean numbers of carious surfaces restored were similar in both groups. A battery of full-scale IQ tests, as well as other neurobehavioural tests, were not different between groups. Although it is possible that very small IQ effects cannot be ruled out, these findings suggest that the health effects of amalgam restorations in children need not be the basis of treatment decisions when choosing dental materials. This is particularly important for areas in the USA as well as other countries, where the replacement of mercury amalgam with a composite restoration material may not be feasible with respect to factors such as cost, storage, and expertise, and thus could adversely affect the dental and general health of the paediatric population.

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