Table 3 Theophylline derivatives and apnoea due to other causes

Citation	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Henderson-Smart and Steer (2001)	192 preterm infants in 5 trials	Systematic review (level 1a)	Reduction in apnoea and use of IPPV	RRR for apnoea 0.45 (95% CI 0.31–0.60). RRR for IPPV 0.34 (95% CI 0.12–0.97)	3 studies used caffeine and 2 studies theophylline
Henderson-Smart and Steer (2001)	78 ex-preterm infants undergoing general anaesthesia for surgery. Gestational age 30–32 weeks. Post conceptual age 40–44 weeks	Systematic review (level 1a)	Reduction in the incidence of apnoea and bradycardia in the postoperative period	RRR 91% (95%CI 66 to 98). ARR 58%. No infant in either control or treatment group required intubation	Intravenous caffeine in a single dose during general anaesthesia. Dosage 5–10 mg/kg
Lim <i>et al</i> (2003)	42 term infants requiring PGE1 infusion for duct dependent congenital heart disease	RCT (level 1b)	Reduction in intubation for apnoea	6/21 required intubation in the placebo compared to 0/21 in the aminophylline group (p=0.02)	6 mg/kg iv aminophylline followed by 2 mg/kg iv 8 hourly for 72 hours

and apnoea/apnea and caffeine/xanthine/methylxanthine/phosphodiesterase inhibitors/theophylline

There was one retrospective review³ and two case reports^{4,5} (in the form of letters to the editor) directly addressing the problem (table 2). There was also one randomised controlled trial on the usefulness of aminophylline in reducing apnoeas and intubation in term infants during prostaglandin E1 infusion.⁶

Searches were performed in August 2004.

Commentary

Recurrent apnoea is a common problem in otherwise well preterm infants. By term equivalent age, infants have usually “outgrown” their tendency to spontaneous apnoea. However, with an additional stress, such as infection (for example, bronchiolitis) or administration of drugs that depress the central nervous system (for example, general anaesthesia, prostaglandin), then apnoea and oxygen desaturations can recur.

Caffeine is recognised to reduce apnoea and the need for mechanical ventilation in preterm infants with apnoea of prematurity.¹ In addition caffeine prevents apnoea, bradycardia, and episodes of desaturation in growing preterm infants following general anaesthesia,² while aminophylline, which is another widely used theophylline derivative, was found to be effective for the prevention of apnoea and intubation during prostaglandin E1 infusion in term infants⁶ (table 3). While these data are supportive, there may be significant differences in the mechanism of apnoea in general anaesthesia and viral induced apnoea.

We could only find three reports^{3–5} involving a total of 10 infants, all of whom were born preterm and presented with bronchiolitis associated apnoeas approximately around term equivalent age. These reports have concluded that theophylline derivatives are effective in reducing the incidence of apnoeas and avoided the need for mechanical ventilation in this clinical situation (table 1).

Caffeine has a more favourable therapeutic index than aminophylline. No major adverse effects were reported from the studies included in the systematic reviews.^{1,2} Jitteriness, tachycardia, and raised blood glucose are the common side effects, but routine drug level monitoring is not necessary at standard dosage.⁷

While these three reports claim that the use of caffeine helped avoid intubation in infants with viral infection induced apnoea, there are no data from randomised controlled trials confirming these benefits. As intubation for

apnoea in bronchiolitis is uncommon, a large multicentre trial would be needed.

CLINICAL BOTTOM LINE

- In addition to its proven efficacy in apnoea of prematurity, caffeine has also been shown to reduce the incidence of apnoea in ex-preterm infants following general anaesthesia and in term infants following prostaglandin infusion.
- There is only limited evidence from case reports for the use of caffeine in infants presenting with bronchiolitis associated apnoeas.

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Are newer macrolides effective in eradicating carriage of pertussis?

Report by

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You are assessing a toddler who has presented with paroxysmal cough with a whoop and post-tussive vomiting. A clinical diagnosis of “whooping cough” is made and this is duly confirmed on pernasal swab cultures that reveal the growth of *Bordetella pertussis*.

From history, you note that he is allergic to penicillin and has been given erythromycin for a previous episode of

Table 4 Use of newer macrolides in pertussis

Citation	Study group	Level of evidence	Outcome	Key results	Comments
Langley <i>et al</i> (2004)	477 children (6 mth–16 y) with clinical symptoms of pertussis were randomised to receive either azithromycin (10 mg/kg on day 1 followed by 5 mg/kg once a day for 4 more days) or erythromycin estolate (40 mg/kg/day in 3 divided doses for 10 days)	Multicentre randomised controlled trial (level 1b)	Bacteriologic eradication: Negative cultures at the end of treatment Relapse: Positive cultures a week after end of treatment Adverse GI events: (parent completed diary)	Azithromycin group: 53/53 v erythromycin group: 53/53 (eradication 100%. 95% CI 93.3–100) Azithromycin group: 0/51 (0%; 95% CI: 0–7.0) v erythromycin group: 0/53 (0%; 95% CI: 0–6.7) Azithromycin v erythromycin groups: Overall incidence of GI side effects was 18.8% v 41.2%, NNT= 4.46 Nausea (2.9% v 8.4%; 95% CI: –8.9% to –2.0%; NNT 18.1), vomiting (5.0% v 13.0%; 95% CI: –4.9% to –1.4% ; NNT= 12.5) Diarrhoea (7.1% v 11.8%; 95% CI: –9.0% to –0.3%; NNT= 21.2) No serious adverse events were recorded in either group 90% in the azithromycin group v 55% in the erythromycin group	Group assignment not blinded after randomisation Positive Nasopharyngeal (NP) cultures for pertussis were found in 58/239 (azithromycin group) and in 56/238 (erythromycin group) Post treatment cultures not available on all subjects
Lebel and Mehra (2001)	153 children (<16 y) with clinical symptoms of pertussis received either clarithromycin 7.5 mg/kg/dose twice a day for 7 days (n=76) or erythromycin (13.3 mg/kg/dose three times a day for 14 days (n =77)	Prospective randomised single blind trial. (level 1b)	Bacteriologic eradication: Negative post treatment cultures Adverse GI events Compliance: (inspection of medication containers)	Negative post treatment cultures recorded in 31/31 on clarithromycin (100%; 95% CI: 88.8–100) v 22/23 with erythromycin (96%; 95% CI: 78.1–99.9%) Seen in 45% of those on Clarithromycin Vs 62% of those on Erythromycin. (p=0.035; NNT= 5.8) Mean percent of drug taken by the Clarithromycin group was 98.5% Vs 88.8% by the Erythromycin group (p<0.001)	35/76 in the clarithromycin group and 27/77 in the erythromycin group had positive cultures of <i>B pertussis</i> 90% of subjects were appropriately immunised against pertussis Post treatment cultures not available on all subjects
Pichichero <i>et al</i> (2003)	34 subjects (29 culture positive and 5 pcr positive) were all given azithromycin (10 mg/kg on day1 followed by 5 mg/kg once a day for 4 more days)	Prospective, open labelled, non comparative trial (level 2b)	Bacteriologic eradication: Negative cultures/ PCR at days 2–3 of treatment and days 14–21 post treatment Adverse events Compliance	1/34 (3%) had positive cultures at 2–3 days on treatment Bacteriologic eradication 97% at 2–3 days and 100% by 14–21 days after starting treatment No serious adverse events recorded 10% patients had GI side effects (nausea, loose stools, and abdominal discomfort) Reported 100%	Study group heterogeneous. No subset analysis available 5 of the 34 subjects were adults (parents of children), 12 were between 10–20 y of age and 17 were from the age of 6 mth to 10 y
Bace <i>et al</i> (1999)	37 subjects with culture proven pertussis. Mean age of patients 7.5 mth (range 2–18 mth). 60% of them were not immunised against pertussis. All received azithromycin. Dose: 10 mg/kg on day1 followed by 5 mg/kg once a day for 4 more days (n= 17) v 10 mg/kg once daily for 3 days only (n= 20)	Prospective, open labelled, non-comparative trial (level 2b)	Bacteriologic eradication: Negative cultures on day 7, 14 after commencement of treatment. Relapse: Positive cultures on day 21 after start of treatment Adverse events	Positive cultures on day 7: 2/19 in the 3 day group (10.5%) v 0/16 in the 5 day group. 100% bacterial eradication was seen on day 14 (0/16 v 0/16) in both groups 1/14 patients on the 3 day course (7.1%). None on the 5 day course Transient increase in liver enzyme ALT noted in up to 20.6% of all subjects	Allocation criteria to either regime unclear Relationship of transaminitis to dose used unclear
Aoyama <i>et al</i> (1996)	17 patients (0– 13 y) with culture proven pertussis 8/17 received azithromycin (10 mg/kg once a day for 5 days) while 9/17 received clarithromycin (10 mg/kg/day in two divided doses for 7 days). Each study subject was matched with two historical controls treated with erythromycin (40–50 mg/kg/day in three divided doses for 14 days) 58.8% of subjects were not immunised against pertussis	Two separate open labelled trials using historical controls (level 4)	Bacterial eradication: negative culture on 1 week after treatment Relapse: positive culture at 2 weeks after treatment	8/8 with azithromycin (100%, 95% CI: 68.8–100%) v 13/16 (81%, 95% CI: 54.4–96%) among controls given erythromycin 9/9 with clarithromycin (100%, 95% CI: 71.1–100%) v 16/18 (88.8%, 95% CI: 65.3–98.6%) among controls given erythromycin None in either study or control groups	Historical controls Allocation criteria to medications unclear Small study group

tonsillo-pharyngitis. His mother recalls that he suffered severe abdominal pain when taking it and did not complete the course. You wonder whether newer macrolides such as azithromycin or clarithromycin could be effective alternatives to erythromycin for the treatment of pertussis.

Structured clinical question

In a child diagnosed with whooping cough [patient] are azithromycin or clarithromycin [intervention] compared with erythromycin [comparison] as effective in eradicating infection with fewer side effects [outcome]?

Search strategy

Primary source: Medline via Pubmed using keywords Pertussis OR Whooping Cough and combining the search with Azithromycin, Clarithromycin separately. This was verified by an alternative search method using MeSH heading "Whooping Cough" and subheading "drug therapy" [MeSH]. Five relevant articles were found.

Secondary sources: Cochrane database and Best Bets. No further papers were identified.

See table 4.

Commentary

Antimicrobials are usually administered when pertussis is suspected or confirmed. If the disease is already established (paroxysmal phase), antibiotics have little or no effect on the clinical course of the illness except to render the patient non-infectious to others. This is important, so as to limit the spread of infection especially to the unimmunised and young infants. A 10–14 day course of erythromycin is the long established treatment for whooping cough.¹ It is known to reduce transmission and hasten clearance of *B pertussis*.³ However, gastrointestinal side effects seem quite limiting in a large proportion of patients treated with it.⁷ This may have a bearing in ensuring compliance. Newer macrolides—clarithromycin and azithromycin—are superior to erythromycin in terms of absorption, acid stability, and tissue penetration. They have longer half-lives, enabling less frequent dosing and shorter treatment courses.⁵ They are also known to have fewer side effects.

From the available evidence it can be seen that the newer macrolides are at least as effective as erythromycin in eradicating *B pertussis* infection. A significant reduction in adverse gastrointestinal side effects and a better compliance have been shown. No serious side effects have been observed

with these agents so far. Transient elevation in alanine aminotransferase (ALT) has been shown in one study.³

Regarding prophylaxis, the current UK guideline is to administer a seven day course of erythromycin, if a clinically suspected or confirmed case of pertussis is identified. The aim is to protect those at risk from pertussis: infants, especially neonates; all household contacts who are unimmunised; and contacts who are 5 years or older if they did not receive a pre-school pertussis booster. There is no evidence of any benefit from chemoprophylaxis given more than 21 days from the date of onset of the primary case. Unimmunised or partially immunised cases and contacts should complete their course of vaccine.⁸ Clarithromycin and azithromycin are potential, but not proven alternatives to erythromycin for prophylaxis at present.

CLINICAL BOTTOM LINE

- A five day course of azithromycin or a seven day course of clarithromycin is as effective as a 10–14 day course of erythromycin to eradicate *B pertussis* infection. (Grade A)
- Azithromycin and clarithromycin have fewer gastrointestinal side effects than erythromycin. (Grade A)
- Patient compliance is better on the newer macrolides compared to erythromycin. (Grade A)

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