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Low-dose budesonide improved asthma control in mild asthma; adding formoterol improved control in corticosteroid-treated patients

A randomised, blinded placebo-controlled trial with 1-year follow-up was carried out to determine whether, in patients with mild asthma, regular low doses of inhaled budesonide, with or without low doses of inhaled formoterol, would reduce severe exacerbations and improve asthma control.

In 198 centres in 17 countries, 1 970 patients were enrolled into the trial.They were ≥ 12 years of age and had mild asthma. Of these, 698 were corticosteroid-free (group A) (mean age 31 years, 60% women), had not used an inhaled corticosteroid for ≥ 3 months and had an FEV_1 ≥ 80% of predicted normal after inhaling terbutaline 1 mg. Group B included 1 272 corticosteroid-treated patients (mean age 37 years, 57% women) who were receiving ≤ 400 µg/d of inhaled budesonide or the equivalent for ≥ 3 months, with an FEV_1 ≥ 70% of predicted normal after terbutaline.

During a 4-week run-in period, group A patients received placebo and group B patients received budesonide 100 µg twice daily. Patients were then allocated to twice daily treatment for 1 year. Group A patients were allocated to

- budesonide 100 µg (*N* = 228)
- budesonide 100 µg, plus formoterol 4.5 µg (*N* = 231) or
- placebo (*N* = 239).

Group B patients were allocated to

- budesonide 100 µg (*N* = 322)
- budesonide 100 µg, plus formoterol 4.5 µg (*N* = 323)
- budesonide 200 µg (*N* = 312) or
- budesonide 200 µg, plus formoterol 4.5 µg (*N* = 315).

All doses were delivered twice daily by Bricanyl Turbuhaler (AstraZeneca, Lund, Sweden), and stated doses were metered doses for budesonide and delivered doses for formoterol.

Main outcomes were time to first severe asthma exacerbation, i.e. need for treatment with oral corticosteroids, hospital admission or emergency treatment for worsening asthma, or a decrease in morning peak expiratory flow rate [PEFR] > 25% from baseline on 2 consecutive days and poorly controlled asthma days (with morning PEFR ≥ 20% below baseline, use of rescue medication ≥ 2 days above baseline, or nocturnal awakening by asthma).

Results

Among group A patients, budesonide 100 µg twice daily reduced the risk for a first severe asthma exacerbation and the rate of poorly controlled asthma days more than did placebo. Adding formoterol to budesonide did not affect these two outcomes.

Among group B patients, budesonide 100 µg and 200 µg twice daily did not differ for risk for a first severe exacerbation or for rate of poorly controlled asthma days. Adding formoterol to budesonide 100 µg or 200 µg, reduced the risk for a first asthma exacerbation and the rate of poorly controlled asthma days. Budesonide 100 µg plus formoterol twice daily was more effective than budesonide 200 µg twice daily for reducing the risk for a severe exacerbation day or a poorly controlled asthma day.

Conclusions

In corticosteroid-free patients with mild asthma, budesonide 100 µg twice daily reduced severe exacerbations and poorly controlled asthma days; the addition of formoterol conferred no added benefit. In patients already receiving inhaled corticosteroids, adding formoterol 100 µg twice daily to budesonide was better than doubling the dose of budesonide.

O'Byrne PM *et al. Am J Respir Crit Care Med.* 2001;**164:** 1392-1397 quoted in *ACP Journal Club* 2002; **137:** 19.

Antibiotics improve maternal and fetal outcomes and are safe in preterm, prelabour rupture of membranes

Preterm birth, with or without rupture of membranes, is a major problem in obstetric and neonatal care. It contributes significantly to maternal morbidity and perinatal morbidity and mortality. Infection has generally been implicated in the cause of preterm labour, but it is of special concern in threatened preterm labour because of ruptured membranes.

A systematic review published evaluated the effectiveness and safety of antibiotics for maternal and fetal outcomes in women with preterm, prelabour rupture of membranes.[1] Studies were identified by searching MEDLINE (from 1966), the Cochrane Controlled Trials Register, key journals, and conference proceedings. Where possible, unpublished data were sought from investigators.

Studies were selected if they were randomised controlled trials, compared antibiotic use with placebo or different antibiotic regimens, included women with preterm (defined as < 37 weeks) rupture of membranes, and reported clinically relevant outcomes.

Results

Thirty-two trials were identified, and 13 trials that randomised > 6 000 women and their babies were included in the review. Most trials were small, except for 2 large trials (1 with 4 826 and 1 with 614 women). Women were recruited between 20 and 37 weeks' gestation, and most women were not in active labour. Nine trials tested broad-spectrum penicillin alone or in combination, 5 tested β-lactam antibiotics alone or in combination, and 1 tested clindamycin and gentamicin. Five trials used oral antibiotics alone, 2 used intravenous antibiotics alone, and 6 used a combination of oral and intravenous antibiotics. Any antibiotic, especially a macrolide antibiotic, was associated with greater improvements in maternal and fetal outcomes than placebo. β-lactam antibiotics were associated with greater neonatal necrotising enterocolitis risk than was placebo. No evidence existed for major adverse drug reactions.

Conclusions

In women with preterm, prelabour rupture of membranes, antibiotics are generally safe and improve maternal and fetal outcomes. Macrolide antibiotics are associated with improved outcomes. β-lactam antibiotics are associated with increased neonatal necrotising enterocolitis.

Khalid S Khan, Birmingham Women's Hospital, Birmingham, England, UK, comments: Clinicians have been ambivalent about the effectiveness of antibiotics among women with ruptured membranes who do not have other signs of infection.[2] The review by Kenyon and colleagues collated and aggregated high-quality evidence, and from its meta-analyses we can be confident that antibiotics are associated with reduced maternal and neonatal morbidity in preterm, prelabour rupture of membranes. However, this message comes with a warning about β-lactam antibiotics.

Can we believe that β-lactam antibiotics increase the risk for necrotising enterocolitis? Subgroup analyses should be interpreted with caution. By reducing the number of trials per subgroup, such analyses run into problems with reduced power, risking an inability to detect a difference when one exists (type II error). However, by increasing the number of comparisons in a review, problems with spurious significance may arise, thereby risking detection of differences that do not exist (type I error). We can be certain about the effect observed in a subgroup analysis if a biological rationale for the effect exists, the effect is large, the subgroup analysis is planned in advance, and the analysis is one of a small number of subgroup analyses. Answers to these questions may not be immediately apparent. In summary, the safest inference is that macrolide antibiotics should be recommended for patients with threatened preterm labour with ruptured membranes.

1. Kenyon S *et al*. *Cochrane Database Syst Rev* 2002; (1):CD001058.
2. *ACP Journal Club* 2002; **137:** 30.