Pharmacotherapy — treatment of intermittent asthma with ICSs

Intermittent asthma is a common pattern in infants and children.[1] Episodes are most often triggered by viral, upper respiratory tract infections (URTIs).[2] Treatment of URTI-associated wheeze in infants and young children is particularly problematic because this form of asthma is less likely to be associated with atopy, appears to have a different natural history[3] and its optimal therapy has not been clearly determined. Because children with intermittent asthma are asymptomatic between episodes, treating exacerbations with short courses of ICSs, thus minimizing exposure to inhaled and systemic exogenous steroids, would appear to be an attractive option.

Literature review

A MEDLINE search for relevant articles was carried out using the terms "glucocorticoids, topical" and "asthma" and "intermittent." Synonyms for "intermittent" including "periodic," "occasional," "sporadic," "interrupted," "cyclic" and "infrequent" were obtained using the ARTFL Project, Roget's Thesaurus and Merriam-Webster Online, and the search was repeated. One additional article was found in electronic abstracts from the American Thoracic Society Meetings 1998–2002, using the same search strategy. The Cochrane Library was also searched using the above text words, as well as "wheezing." The bibliography of each identified article was searched for relevant papers. The choice of articles to review was confirmed by consensus among the co-authors.

Articles relating to this topic published through to December 2004 were also reviewed, but contained insufficient data to modify the recommendations.

Current evidence

Although few articles have examined the efficacy of intermittent therapy with ICSs, this management strategy appears to be prevalent in Canada. One survey indicated that 55% of children with asthma use and 48% of adults with asthma use inhaled corticosteroids "when getting an attack or having difficulty breathing."[4] Only 43% of children use inhaled corticosteroids everyday on a regular basis to help control asthma.[4] In our literature review, we found only 5 articles and 1 abstract that address this issue. These studies all used metered-dose inhalers and spacers, except where otherwise noted.

Wilson and Silverman[5] enrolled 35 children with asthma aged 1–5 years (mean age 3.5 years) in a double-blind crossover study in which they were given beclomethasone, 750 µg 3 times daily for 5 days, or placebo for use during asthma exacerbations. Twenty-four children completed the trial. Beclomethasone had no significant effect on admissions to hospital or need for prednisone. Symptom scores were significantly lower with active treatment both at night and during the day during the first week, but not during the second week. Symptoms were relatively mild in all children, but decreased significantly in the first week: scores were 1.36 in the placebo group and 0.92 in the active treatment group. The duration of symptoms was similar in both groups. Virtually all episodes appeared to be related to viral URTI. The authors questioned whether the older spacer design used in this study provided adequate drug delivery, potentially reducing the treatment effect. Overall, 19 of 35 parents in the active treatment group thought that the treatment helped versus 9 of 35 in the placebo group.

Connett and Lenney[6] enrolled 32 children, aged 1–5 years (mean age 3.5 years) with a history of wheezing associated with URTI, in a double-blind crossover study. The children were given budesonide, 800 µg twice daily by spacer with mouthpiece (or 1600 µg twice daily by spacer with mask) or placebo, until symptoms had resolved, or for 7 days. Each drug was given for 1 episode. If prednisone was needed, subjects could re-enroll for an additional pair of treatments. Twenty-five children completed the study. Children tended to require prednisone more often during placebo treatment (8 v. 2 courses of treatment among 28 treatment pairs). During the first week of a URTI, daytime and nighttime wheezing scores were significantly lower during treatment with budesonide. Cough symptom scores and bronchodilator use was similar for both treatments. Parents' preference for the active treatment was significant.

Svedmyr and colleagues[7] enrolled 31 children with asthma known to deteriorate with URTI in a double-blind crossover study. They were given budesonide, 200 µg 4 times daily by Turbuhaler, tapered over 9 days or placebo for use during asthma exacerbations triggered by a URTI. Twenty-two children completed the study; their ages ranged from 3 to 10 years (mean 5.3 years). About half the participants used sodium cromoglycate concurrently. Most of the children were atopic. Morning and evening PEF values were significantly higher during treatment with budesonide than with placebo (104% v. 96% of predicted, respectively). Symptom scores were similar in the 2 groups. Emergency department visits tended to be fewer during treatment with budesonide (3 v. 8 visits) and oral steroid use (with or without admission to hospital) was significantly lower during active treatment (0 v. 5 times), although this was not stated in the article.

In a subsequent study,[8] 55 children 1–3 years of age (mean age about 2 years) with asthma exacerbated by URTI were enrolled for a randomized, double-blind, parallel group study of budesonide, 400 μg 4 times daily, tapered over 10 days, or placebo. The study lasted up to 12 months. A quarter of the children were atopic. Total and daytime asthma symptom scores were significantly lower in the active treatment group (0.38 v. 0.55), and nighttime symptoms tended to be less severe. Cough, sleep disturbance and noisy breathing scores were significantly lower with budesonide, and wheezing and dyspnea scores tended to be lower as well. Oral steroid use, visits to the emergency department, admissions to hospital and bronchodilator use were similar in the 2 groups.

In a study by Volovitz and coworkers,[9] 193 children, ranging in age from 1 to 16 years, received budesonide, 200–400 μg 4 times daily tapered over 4–8 days, during acute exacerbations, then budesonide, 100 μg twice daily, until they were symptom-free for 6–8 weeks. If, after that time, they remained asymptomatic for 3 weeks, they used budesonide only during exacerbations. One hundred and fifty children completed the study. MDI and spacers were used in younger children and Turbuhalers in children over 7 years of age. Children were followed for an average of 1 year. Oral corticosteroids appeared to be needed less frequently (7% v. 67% of the children) and there were fewer admissions to hospital (0% v. 33%) during the 1-year follow-up than in the 3 months before enrolment in the study. There was no control group in this study, rates of events and statistics were not provided and the authors do not account for any potential spontaneous improvement in the natural history of URTI-associated asthma.

In a study[10] of 413 adults with asthma (mean age 43 years; 403 completed the study) received a tapering course of prednisolone, starting with 40 mg, or fluticasone, 1000 μg twice daily for 16 days, for an asthma exacerbation judged severe enough to require oral steroids, but not severe enough to require admission to hospital. About 3 in 4 participants were using ICSs at study entry at a median dose of 800 μg/day. Improvements in PEF and symptoms were similar in the 2 groups, although the oral prednisolone dose used was relatively low. The proportion of treatment "failures" was also similar (22.7% with prednisolone v. 27% with fluticasone).

In a study[11] in children (n = 55, age range 5–12 years) reported only in abstract form, fluticasone, 500 μg twice daily for 10 days, oral prednisone for 5 days and placebo were compared in terms of prevention of asthma exacerbations associated with URTI in children with mild asthma. During the 2 weeks of treatment, morning PEFs were significantly lower with placebo than with fluticasone or prednisone (221, 254 and 234 L/minute respectively), but rescue bronchodilator use was similar in all 3 groups (17, 18 and 15 doses/week, respectively).

Nuhoglu and colleagues[12] compared the effectiveness of budesonide, 400 μg 4 times daily, with oral methylprednisolone in 60 children with asthma, aged 4–17 years, during an acute exacerbation not requiring hospital admission, but unresponsive to bronchodilator use alone. Treatment was continued for 3 days, and accompanied by mandatory use of a bronchodilator 4 times a day. The patients' mean age was about 9 years, and just under 50% were taking prophylactic inhaled steroids. The clinical score improved significantly more in the high-dose inhaled steroid group (2.6 v. 1.9), and pulmonary function improved significantly in both groups (13.7% and 13.4% improvement).

Hedlin and colleagues[13] examined the systemic effects of a short course of inhaled steroids compared with systemic steroids in a companion paper to their 1999 study,[8] using a portion of the original study population. No significant changes in serum cortisol, osteocalcin, bone markers, or urine cortisol–creatinine ratio occurred after treatment with budesonide, but significant changes in all of these levels, save serum cortisol, occurred with oral betamethasone.

Brieva and coworkers[14] reported that in 31 adults (average age 36 years), fluticasone, 250 μg twice daily for 2 weeks, significantly reduced airway mucosal blood flow (by 11.3%) resulting in more normal values. Patients with asthma were noted to have a blunted vasodilator response to salbutamol, which normalized after administration of fluticasone, suggesting reversal of a previous downregulation of β–receptor function. The authors suggest that intermittent therapy may have some effect on airway physiology. Unfortunately, no similar data are available for a pediatric population.

In a study of 52 adults, aged 20–50 years, Convery and colleagues[15] reported that an improvement in methacholine responsiveness conferred by fluticasone, 2000 μg daily for 6 weeks, dissipated within 2 weeks of stopping therapy, suggesting that intermittent or "pulse" therapy was unlikely to be effective in providing long-term asthma control.

Discussion

High-dose inhaled steroids given intermittently for asthma triggered by URTI appear to reduce asthma symptom scores, although duration of symptoms does not appear to be altered. The effect on symptom scores was generally small and may not be clinically significant. Similarly, intermittent high-dose inhaled steroids appear to improve pulmonary function, including PEF rates; however, more clinically important outcomes, including visits to emergency departments, admissions to hospital and a requirement for systemic steroids do not appear to be affected. Trials reported in the literature may have been too small to detect a small, but real, effect. It should be noted that regular treatment with inhaled steroids has been shown to improve these asthma outcomes in many high-quality trials in children, where most of the exacerbations were almost certainly triggered by viral URTIs.[2,16–18] Although short courses of systemic steroid also appear to prevent severe exacerbations,[19] repeated courses of oral steroids may have

greater systemic effects than regular therapy with usual doses of inhaled steroids.[20] Systemic effects from intermittent high-dose inhaled steroids appear to be low, although the evidence to confirm this is minimal. Nuhoglu and colleagues[12] speculated that the rapid effects several studies have noted with high-dose inhaled steroids may be due to the rapid mucosal blanching resulting from reduction in mucosal edema and vasoconstriction produced by topical application of high-potency glucocorticoids.

In a recent review of this subject, conclusions similar to ours were reached by Hendeles and Sherman[21] who noted that inhaled steroids, "if started early and in high doses, provide modest benefit in the acute treatment of patients with mild exacerbations of asthma. At home, early institution prevented neither the need for intervention with oral corticosteroid nor hospital admission in young children with virus-induced asthma." However, somewhat conflicting findings were reported in a Cochrane review of inhaled steroids for episodic viral wheezing.[22] This meta-analysis contrasted reports from Connett and Lenney,[6] Wilson and Silverman[5] and Svedmyr and colleagues[8] with 2 studies[23,24] that used regular treatment with conventional doses of inhaled steroids in children with recurrent wheezing associated with viral URTIs. However, the participants in 1 of the 2-comparator trials had a history of parent-reported wheezing, and it is unclear whether these patients had asthma or recurrent, true wheezing. McKean and Ducharme[22] concluded that "there is no evidence to suggest that a low daily dose of inhaled corticosteroid is beneficial in the prophylaxis of mild episodic viral wheeze. Conversely, high-dose episodic inhaled corticosteroids appear partially effective in preventing or attenuating viral-induced episode in children with predominantly mild episodes." A recent placebo-controlled crossover trial of regular treatment with fluticasone in children with intermittent wheeze[25] reported a significant improvement in airway resistance measured by the interrupter technique with active treatment.

Treatment of children with intermittent courses of inhaled steroids has become a "community standard." Regular use of low-dose inhaled steroids is currently the recommended treatment for children, even those with intermittent asthma symptoms. The use of intermittent treatment as a strategy for management of intermittent asthma in childhood requires further validation, particularly in very young children.[26]

Implications for research

1. Large, randomized, placebo-controlled trials should evaluate the effect of intermittent treatment with high-dose inhaled steroids on important health outcomes, including the need for prednisone, visits to emergency department and admission to hospital.
2. Studies should compare the efficacy and safety of intermittent treatment with high-dose inhaled steroids compared with regular therapy with conventional doses of inhaled steroids, particularly for children with intermittent asthma triggered by viral URTI.

Implementation strategies

1. Community physicians will need to be aware that intermittent treatment with high-dose inhaled steroids appears to have fairly minimal clinical effect, and in children placed on this form of therapy, careful monitoring is essential to verify that the treatment is successful at achieving acceptable asthma control.
2. Further efforts are required to increase the awareness of community physicians that children who fail this form of therapy or who have more severe asthma must be treated with inhaled steroids administered on a long-term basis, at least during the season(s) when the child is at risk of asthma exacerbations.

References

1. Phelan PD, Landau LI, Olinsky A. *Respiratory illness in children*. 3rd ed. Oxford: Blackwell; 1990.
2. Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, et al. Community study of role of viral infections in exacerbations of asthma in 9–11 year old children. *BMJ* 1995;310(6989):1225-9.
3. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med* 2000;343(8):538-43.
4. Asthma in Canada: a landmark survey. Mississauga (ON): Glaxo Wellcome Inc. Executive summery available: www.asthmaincanada.com/manage/execsumm_en.pdf (accessed 2005 Jul 6).
5. Wilson NM, Silverman M. Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home. *Arch Dis Child* 1990;65(4):407-10.
6. Connett G, Lenney W. Prevention of viral induced asthma attacks using inhaled budesonide. *Arch Dis Child* 1993;68(1):85-7.
7. Svedmyr J, Nyberg E, Asbrink-Nilsson E, Hedlin G. Intermittent treatment with inhaled steroids for deterioration of asthma due to upper respiratory tract infections. *Acta Paediatr* 1995;84(8):884-8.
8. Svedmyr J, Nyberg E, Thunqvist P, Asbrink-Nilsson E, Hedlin G. Prophylactic intermittent treatment with inhaled corticosteroids of asthma exacerbations due to airway infections in toddlers. *Acta Paediatr* 1999;88(1):42-7.
9. Volovitz B, Nussinovitch M, Finkelstein Y, Harel L, Varsano I. Effectiveness of inhaled corticosteroids in controlling acute asthma exacerbations in children at home. *Clin Pediatr (Phila)* 2001;40(2):79-86.
10. Levy ML, Stevenson C, Maslen T. Comparison of short courses of oral prednisolone and fluticasone propionate in the treatment of adults with acute exacerbations of asthma in primary care. *Thorax* 1996;51(11):1087-92.
11. Cox ML, Scurlock JM, Kinrade S, Solterbeck A, Le Souef PN. Intermittent treatment for URTI-induced asthma exacerbations in children [abstract]. *Am J Respir Crit Care Med* 2002;165:A563.
12. Nuhoglu Y, Bahceciler NN, Barlan IB, Mujdat Basaran M. The effectiveness of high-dose inhaled budesonide therapy in the treatment of acute asthma exacerbations in children. *Ann Allergy Asthma Immunol* 2001;86(3):318-22.
13. Hedlin G, Svedmyr J, Ryden AC. Systemic effects of a short course of betamethasone compared with high-dose inhaled budesonide in early childhood asthma. *Acta Paediatr* 1999;88(1):48-51.
14. Brieva JL, Danta I, Wanner A. Effect of an inhaled glucocorticosteroid on airway mucosal blood flow in mild asthma. *Am J Respir Crit Care Med* 2000;161(1):293-6.
15. Convery RP, Leitch DN, Bromly C, Ward RJ, Bartlett G, Hendrick DJ. Effect of inhaled fluticasone propionate on airway responsiveness in treatment-naïve individuals — a lesser benefit in females. *Eur Respir J* 2000;15(1):19-24.
16. Verberne AA, Frost C, Roorda RJ, van der Laag H, Kerrebijn KF. One year treatment with salmeterol compared with beclomethasone in children with asthma. The Dutch Paediatric Asthma Study Group. *Am J Respir Crit Care Med* 1997;156(3 pt 1):688-95.
17. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. *N Engl J Med* 2000;343(15):1054-63.
18. Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, et al.

Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003;361(9363):1071-6.
19. Brunette MG, Lands L, Thibodeau L-P. Childhood asthma: prevention of attacks with short-term corticosteroid treatment of upper respiratory tract infection. *Pediatrics* 1988;81(5):624-9.
20. Dolan LM, Kesarwala HH, Holroyde JC, Fischer TJ. Short-term, high-dose, systemic steroids in children with asthma: the effect on the hypothalamic-pituitary-adrenal axis. *J Allergy Clin Immunol* 1987;80(1):81-7.
21. Hendeles L, Sherman J. Are inhaled corticosteroids effective for acute exacerbations of asthma in children? *J Pediatr* 2003;142(2 suppl):S26-33.
22. McKean M, Ducharme F. Inhaled steroids for episodic viral wheeze of childhood (Cochrane review). In: The Cochrane Library; Issue 1, 2003. Oxford: Update Software.
23. Wilson N, Sloper K, Silverman M. Effect of continuous treatment with topical corticosteroid on episodic viral wheeze in preschool children. *Arch Dis Child* 1995;72(4):317-20.
24. Duoll IJM, Lampe FC, Smith S, Schreiber J, Freezer NJ, Holgate ST. Effect of inhaled corticosteroids on episodes of wheezing associated with viral infection in school age children: randomised double blind placebo controlled trial. *BMJ* 1997;315:858-62.
25. Pao CS, McKenzie S. Randomized controlled trial of fluticasone in preschool children with intermittent wheeze. *Am J Respir Crit Care Med* 2002;166(7):945-9.
26. Boulet LP, Becker A, Berube D, Beveridge R, Ernst P. Summary of recommendations from the Canadian Asthma Consensus Report, 1999. *CMAJ* 1999;161(11 suppl):S1-12.

Copyright of *CMAJ*: Canadian Medical Association Journal is the property of *CMA* Media Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.