ORIGINAL ARTICLE

Inhaled Nedocromil Sodium for Persistent Cough in Children

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Summary

The efficacy of inhaled nedocromil sodium (NS) for children with a persistent cough was studied. Children aged 4 - 12 years with a persistent cough for >1 month were recruited and entered a 2-week baseline period during which an asthma diary was kept. Children with a cough score of >20 received inhaled NS via a spacer, 4mg qid for 2 weeks followed by 4mg bd for another 4 weeks. Twenty-two (42%) of 52 children recruited fulfilled treatment criteria. Four children were withdrawn from the study (2 developed wheezing and 2 were not compliant). The baseline cough score (29.1±13.6) improved after 2 weeks of treatment (15.2±9.3, $p<0.01$) and improvement was sustained after 6 weeks (14.2±13.0, $p=0.01$). Parents and patients had a more favourable perception of its efficacy compared to physicians (72% vs 50%, $p=0.01$)

Inhaled NS may be considered for treatment of persistent cough in children.

Key Words: Persistent cough, Inhaled necrodomil sodium

Introduction

Children with a persistent troublesome cough are a common problem encountered in clinical paediatric practice. In many instances the persistent cough is not associated with a recurrent wheeze. Persistent cough has been increasingly recognised as the sole symptom of childhood asthma resulting on occasions in it being labelled as "cough variant asthma"[1] This diagnostic category may not be too far from the truth as children with a persistent cough have been shown to demonstrate airway hyperesponsiveness to metacholine challenge tests, not unlike the more easily recognised asthmatic subject[2,3]. Asthma treatment guidelines also use persistent cough as a marker of asthma stability or control[4].

Nedocromil sodium, a mast cell stabiliser has been used effectively as an anti-inflammatory agent for asthma prophylaxis, particularly in adult asthmatics. Inhaled nedocromil sodium has not been extensively evaluated for the treatment of children with persistent cough and there is still very little information on its use in Asian children. We therefore set out to determine the efficacy of inhaled nedocromil sodium in Malaysian children with a persistent cough.

Materials and Methods

Subjects

Children aged 4 to 12 years presenting to our unit between 1 January 1999 and 31 December 1999

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with a persistent troublesome cough for more than 4 weeks duration were eligible for recruitment into the study. Children with an established diagnosis of asthma who were receiving less than 400mcg daily of inhaled beclomethasone propionate or budesonide dipropionate (equivalent to 200mcg fluticasone propionate), had no recurrent wheezing and no asthma exacerbation in the last 1 year requiring systemic steroid or hospitalisation were also eligible for recruitment. Children who had any other disease than asthma that may cause a cough or with renal, cardiovascular or hepatic disease were excluded. Children, who had received inhaled sodium cromoglycate, oral ketotifen or leukotriene modifiers within the last 4 weeks prior to the first visit were not eligible for the study. The hospital ethical review committee approved the study protocol and written informed consent was obtained from the parents before enrolment.

Children recruited entered a 2 week baseline period during which their daily cough symptoms were monitored and recorded using a cough diary (Table I). Children who had a cough score of 20 or more at the end of 2 weeks and who still fulfilled the inclusion criteria and none of the exclusion criteria were eligible for treatment with inhaled nedocromil sodium.

Study protocol

The study design was single arm, open labelled and non-comparative treatment with inhaled nedocromil sodium via a spacer device (Fisonair®) for 6 weeks duration. Children received inhaled nedocromil sodium 4mg q.i.d. for 2 weeks followed by 4mg b.d.for another 4 weeks. Children who were enrolled into the treatment trial visited the clinic on 4 occasions; at recruitment, at the end of the 2 week baseline period, after 2 weeks, and 6 weeks of treatment. Throughout the trial, the parents continued to monitor and record cough symptoms with the cough diary. Peak expiratory flow rates (PEFR) were performed for all children above 5 years at each clinic visit. The PEFR reading used was the best of 3 measurement taken standing and done at about

Table I
Daytime and Night Time Symptoms for Daily Cough Score

Daytime cough-score is recorded each evening before going to bed using a 0 - 4 point scale	
Cough	**Point**
No cough during day	0
Occasional cough or exercise induced - not troublesome	1
Frequent cough - did not interfere with usual activities	2
Frequent cough - interfere with usual activities	3
Distressing cough most of the day	4
Night-time cough score is recorded each morning on awakening using 0 - 4 point scale	
Cough	**Point**
No cough during night	0
Occasional cough during the night - does not disturb sleep	1
Woke once during the night because of the cough	2
Woke several times during the night because of the cough	3
Kept awake most of the night because of cough	4

the same time for each clinic visit. The PEFR was then expressed as ratio [PEFR(r)] to the expected PEFR for the age and height of healthy Malaysian children[5]. Treatment response was determined with the cough score, PEFR and parental and physician perception of its efficacy.

Global opinion of efficacy

Parents were asked at the end of 2 and 6 weeks of treatment to grade the overall efficacy of the treatment using a five point scale where 0=very effective, 1=moderately effective, 2=slightly effective, 3=no effect and 4=made condition worse. The perception of its efficacy as assessed by the attending physician was also recorded using this five-point scale.

Global liking of study product

Children and parents were asked to grade the degree of their liking of inhaled nedocromil sodium using a scale of a minimum of 1 to a maximum of 10 with 1 indicating a total dislike of the drug and 10 if the child liked it very much.

Adverse experiences

Children and parents were asked to report any adverse event encountered during the study to the investigators within 24 hours of the onset of the adverse experience. Adverse experiences were defined as asthma related events i.e. wheezing, asthma exacerbation requiring systemic corticosteroids or hospitalization and non-asthma related events. The occurrence of an asthma related event resulted in exclusion from the study. All adverse events were then evaluated by the investigators after which an adverse experience (AE) form was completed. The research liaison monitor was also promptly notified.

Statistical analysis

Data collected was analysed with SPSS (SPSS Inc., Chicago, III., USA) statistical programme version 7.0 using Windows 98 operating systems. The mean values of the cough score for every subsequent 2-week period of treatment was compared to the baseline period using the paired samples students t test. Dichotomous variables were compared with the Fishers exact test. A p value of less than 0.05 was considered as significant.

Results

A total of 52 children fulfilled the inclusion criteria and entered the 2-week baseline period. Twenty-two (42%) children fulfilled the baseline cough score criteria for treatment with inhaled nedocromil sodium. Four children were subsequently withdrawn as 2 children developed recurrent wheezing and another 2 were not compliant to treatment. Ten girls and 8 boys completed the study with a median age of 6.0 years. There were 9 Malays, 5 Chinese and 4 Indians. Eight children had an established diagnosis of asthma and were on inhaled corticosteroids.

There was significant improvement from the baseline cough score after 2 weeks of treatment ($p=0.001$) and this improvement was sustained after 6 weeks of treatment ($p=0.01$) (Figure 1). Two (11%) children did not improved with inhaled nedocromil sodium and were started on inhaled corticosteroids at the end of the study. PEFR readings were available in 12 children. There was also significant improvement in the PEFR(r) after 6 weeks of treatment with inhaled nedocromil sodium (mean 1.04±0.19 vs 1.18±0.22, $p=0.01$). There was no difference in the response to inhaled nedocromil sodium between children who had an established diagnosis of asthma receiving inhaled corticosteroids and those who did not (cough score at 6 weeks: 14.4±12.4 vs 14.0±12.2, $p=0.95$).

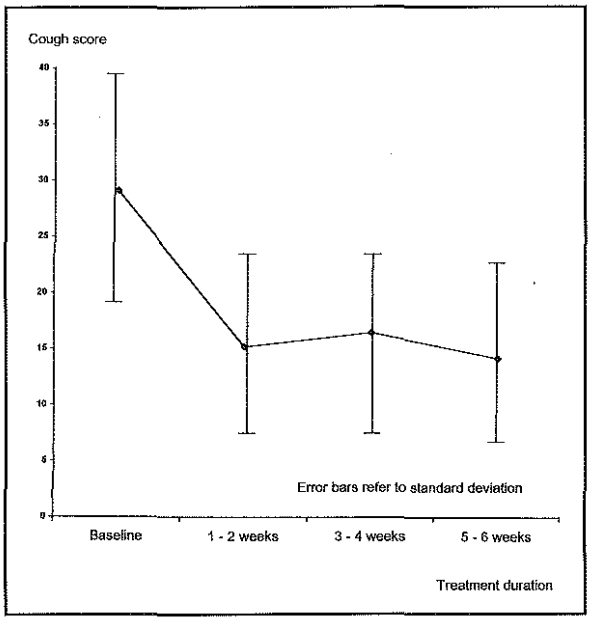

Fig. 1: Treatment with 6 weeks duration of inhaled nedocromil sodium and mean cough score (n=18).

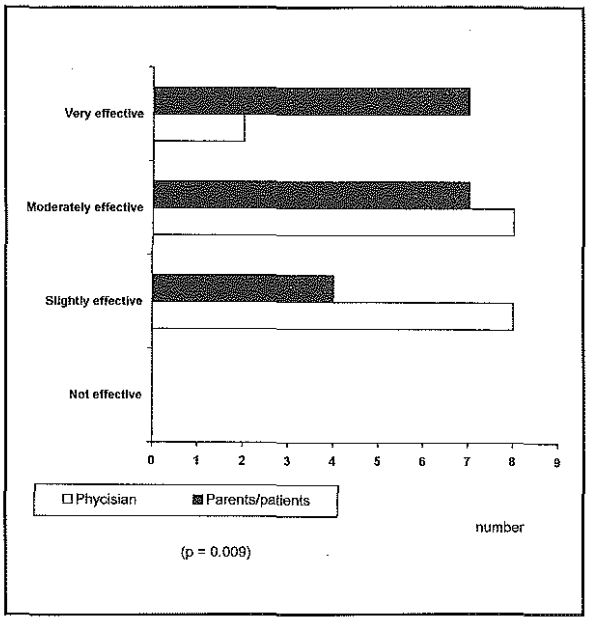

Fig. 2: Perception of the efficacy on inhaled nedocromil sodium by parents/ patients and physicians (n=18).

Parents and patients had a more favourable perception of the efficacy of inhaled nedocromil sodium than the attending physicians did (Figure 2). All except 1 child expressed a liking for the product taste with a mean liking score of 7.9±2.8 (maximum of 10). There were no reported adverse experiences associated with the use of inhaled nedocromil sodium during the study.

Discussion

Nedocromil sodium, a mast cell stabiliser has been shown to be quite effective in inhibiting the inflammatory cascade responsible for asthma symptomology[6,7] and its efficacy in the treatment of asthma has been evaluated extensively in adults with promising results[8,9]. Although its use in children has been less extensive, several studies have nonetheless shown benefit with its use as inhaled prophylaxis in childhood asthma. Its use when compared to a placebo in children has been associated with a reduction in asthma symptoms namely recurrent wheeze, improvement in lung function and reduced dependence on inhaled bronchodilator rescue therapy[10,11,12].

The use of conventional asthma therapy namely inhaled corticosteroids in the treatment of persistent cough in children has been shown to be effective in numerous studies[13,14]. These observations provide further support that persistent cough in children is most likely a variant category of bronchial asthma and make a trial for the use of asthma medication in them acceptable. However, the diagnosis of cough variant asthma or uncontrolled asthma in children with a persistent cough has been increasingly questioned[15,16]. In view of these recent observations, treating childhood persistent cough with inhaled corticosteroids may not be

entirely in the child's best interest; considering the potential side effects associated with its use. Furthermore, the use of inhaled corticosteroids for the treatment of persistent cough in children has not been consistently associated with a beneficial effect[17].

It has been observed that inhaled nedocromil sodium had a more striking therapeutic effect on cough severity in several studies where it was used for the treatment of bronchial asthma[18,19]. A persistent cough is believed to be due to recurrent sensory nerve activation in the bronchial mucosa. The nerve within the airways are exposed as a result of epithelial shedding that occur in asthma or after a lower respiratory tract infection. These exposed nerve endings are easily sensitised and release sensory neuropeptides that then trigger a local axon process in the airway resulting in a cough[20]. There is evidence to indicate that nedocromil sodium inhibits the activation of these airways nerve endings, as it is highly effective against several indirect airway challenge studies that predominantly involve sensory nerve stimulation[21]. Our study demonstrated a beneficial effect with inhaled nedocromil sodium in a selected group of children who had a troublesome persistent cough without significant recurrent wheeze or lung function deterioration. Interestingly, the treatment response was evident after 2 weeks of treatment, as compared with inhaled sodium cromoglycate that may require up to 6 weeks of treatment for benefit. This fairly rapid response to nedocromil sodium is similar to experience reported elsewhere[11,12] and is clearly important to children and parents seeking early symptom alleviation. The treatment response was also similar in children with an established diagnosis of asthma on inhaled corticosteroids who would otherwise have received a higher dose of the inhaled corticosteroids for more satisfactory symptom control. This "steroid-sparing" effect of inhaled nedocromil sodium has been explored in symptomatic adult asthmatics receiving inhaled corticosteroids of 1000mcg/day but did not always yield a beneficial effect[22,23].

Inhaled nedocromil sodium appears to be well tolerated in children, as there were no untoward reactions reported in our study population. As inhale nedocromil sodium has been associated with an unpleasant taste, the drug preparation for our study was masked with a mint aftertaste. All but one child liked and tolerated the drug preparation with an overall excellent liking score.

Inhaled nedocromil sodium has not been evaluated in the manner described in this study and its use in Asian children has not been extensively reported in the literature. Our study was however limited by difficulty in recruiting children that fulfilled both the inclusion criteria and treatment criteria as it involved a very select group of symptomatic children in a single centre. Almost 60% of children who fulfilled the inclusion symptom criteria did not have a persistent cough that fulfilled the need for additional treatment after 2 weeks of careful monitoring using a cough diary. This observation suggests that a number of children with a persistent cough may improve without additional treatment or that a significant number of parents have an inaccurate interpretation of the frequency of cough symptoms in their children. Clearly, a more extensive multi-centre approach in evaluating inhaled nedocromil sodium using a randomised, double blind and placebo controlled study design for this purpose is needed. Nonetheless, it may be worth considering inhaled nedocromil sodium for persistent cough in children in view of the results aforementioned.

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References

1. O'Connell EJ, Rojas AR, Sachs MI. Cough-type asthma: a review. Ann Allergy 1991; 66: 278-85.
2. Cloutier MM, Loughlin GM. Chronic cough in children: a manifestation of airway hyperactivity. Pediatrics 1981; 67: 6-12.
3. Carrao WM, Braman SS, Irwin RS. Chronic cough as the sole presenting manifestation of bronchial asthma. N Eng J Med 1979; 300: 633-7.
4. Rees J, Price J. Asthma in children: treatment. Br Med J [Clin Res] 1995; 310: 1522-8.
5. Azizi BHO, Henry RL. Peak expiratory flow rate of Malaysian children. Med J Malaysian 1991; 46: 82-7.
6. Pearce FL. Effect of nedocromil sodium on mediator release from mast cells. J Allergy Clin Immunol 1993; 92: 155-8.
7. Church MK, Holgate ST. Adenosine-induced bronchoconstriction and its inhibition by nedocromil sodium. J Allergy Clin Immunol 1993; 92: 190-4.
8. Scwartz HJ, Kemp JP, Bianco S, et al. Highlights of the nedocromil sodium clinical study presentations. J Allergy Clin Immunol 1993: 92: 204-9.
9. Edwards AM, Stevens MT. The clinical efficacy of inhaled nedocromil sodium (Tilade) in the treatment of asthma. Eur Respir J 1993; 6: 35-41.
10. Edwards AM, Lyons J, Weinberg, et al. Early use of inhaled nedocromil sodium in children following an acute episode of asthma. Thorax 1999; 54: 308-15.
11. Buscino L, Cantani A, Di Fazio A, et al. A double-blind, placebo-controlled study to assess the efficacy of nedocromil sodium in the management of childhood grass-pollen asthma. Clin Exp Allergy 1990; 20: 683-8.
12. Armenio L, Bardini G, Bardare M, *et al.* Double-blind, placebo-controlled study of nedocromil sodium in asthma. Arch Dis Child 1993; 68: 193-7.
13. Spelman R. Two-year follow up of the management of chronic cough or recurrent cough in children according to an asthma protocol. Br J Gen Practice 1991; 41: 406-9.
14. Cheriyan S, Greenberger PA, Patterson R. Outcome of cough variant asthma treated with inhaled steroids. Ann Allergy 1994; 73: 478-80.
15. McKenzie S. Cough - but is it asthma? Arch Dis Child 1994; 70:1-2
16. Faniran AO, Peat JK, Woolcock AJ. Persistent cough: is it asthma? Arch Dis Child 1998; 79: 411-4.
17. Chang AB, Phelan PD, Carlin J, Sawyer SM, Robertson CF. Randomised controlled trial of inhaled salbutamol and beclomethasone for recurrent cough. Arch Dis Child 1998; 79: 6-11.
18. Grief J, Fink J, Smorzk Y, *et al.* Nedocromil sodium and placebo in the treatment of bronchial asthma: A multivariable, double-blind parallel group comparison. Chest 1989; 96: 583-8.
19. Cherniack RM, Wasserman SI, Ramsdell JW, *et al.* A double-blind multicenter group comparative study of the efficacy and safety of nedocromil sodium in the management of asthma. Chest 1990; 97: 1299-1306.
20. Laitinen LA, Heino M, Laitinen A, Kava T, Haahtela T. Damage of airway epithelium and bronchial reactivity in patients with asthma. Am Rev Respir Dis 1985; 131: 599-606.
21. Barnes PJ. Effect of nedocromil sodium on airway sensory nerves. J Allergy Clin Immunol 1993; 92: 182-6.
22. Svendsen UG, Jorgensen H. Inhaled nedocromil sodium as additional treatment to high dose inhaled corticosteroids in the management of bronchial asthma. Eur Respir J 1991; 4: 992-9.
23. Wong CS, Cooper S, Britten JR, Tattersfield AE. Steroid sparing effect of nedocromil sodium in asthmatic patients on high doses of inhaled steroids. Clin Exp Allergy 1993; 23: 370-6.