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The efficacy and therapeutic position of nedocromil sodium

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Nedocromil Sodium and Adults

Nine major, double-blind, controlled studies of the use of 4 mg nedocromil sodium administered *via* metered dose inhaler (MDI) to adults have been published in full since the first BTS Guidelines review (1–9) (see Table 1). The ages of the treated patients have ranged from 12 to 74 years. These studies have shown clinically and statistically significant effects of 4 mg nedocromil sodium on the daily symptoms of asthma, pulmonary function and concomitant therapy.

Adding 4 mg nedocromil sodium or placebo twice (1) or four times (2) a day to mild to moderate asthma patients exhibiting symptoms, although having access to p.r.n. inhaled and/or oral bronchodilators [high dose (2)], led to significant improvements in asthma summary score, daytime asthma and sleep difficulty due to asthma, despite significantly reduced bronchodilator use. The changes in the symptom scores in the nedocromil-sodium-treated patients were such that they improved to scores lower than those recorded under the maintenance bronchodilator regimen. Maintenance sustained release theophylline and oral and inhaled β_2-bronchodilators had been stopped 2 weeks before the study treatments commenced.

In a similar study (3) in mild to moderate theophylline-dependent patients (except that the sustained release theophylline treatment was halved after 4 weeks of 4 mg nedocromil sodium or placebo twice daily and then removed completely after 6 weeks), addition of nedocromil sodium gave significant improvements in day- and night-time asthma, morning tightness, cough, and day- and night-time inhaled bronchodilator use for most variables from the first period of assessment. Removal of theophylline therapy led to a gradual return of these variables to baseline levels in the nedocromil sodium-treated patients, and a marked deterioration in the placebo-treated patients such that between-treatment differences were highly significant statistically. These and the following data suggest that 4 mg nedocromil sodium two to four times daily can provide equivalent-to-better control of asthma than regular and/or maintenance bronchodilator therapy.

Double-blind, double-dummy comparisons of 4 mg nedocromil sodium with a regular inhaled β_2-bronchodilator (180–200 μg) four times daily (4,5) have shown significant improvements compared with the bronchodilator for day- and night-time asthma symptoms (4,5), morning chest tightness (5), and clinic assessment of daytime asthma, wheezing and shortness of breath (4). In a year-long, placebo-controlled, group comparison of 719 patients treated with 4 mg nedocromil sodium either twice or four times daily, depending on current therapy (bronchodilators only or inhaled steroids, respectively), night-time asthma and daytime inhaled β_2 use were significantly reduced throughout, coupled with improvements in quality-of-life measures of health (6).

Nedocromil sodium has also been shown to be effective in short-term use; adding 4 mg nedocromil sodium under double-blind, placebo-controlled, crossover conditions twice (7) or four times daily (7,8) to patients already on optimal high-dose inhaled steroid therapy (mean daily dose 1462 μg) or remaining symptomatic despite inhaled steroid and oral bronchodilator therapy, led to significant improvements in total (7) and nocturnal (8) symptom scores, cough and morning tightness alongside significantly reduced night-time inhaled β_2-bronchodilator use (7,8). Supportive of these data, a phased steroid-reduction study (9) has shown nedocromil sodium to be of potential use in reducing high-dose inhaled steroid use. Patients requiring 2000 μg inhaled steroid daily reduced this usage by 31% (625 μg daily) after receiving four times daily 4 mg nedocromil sodium compared with placebo.

Compared with placebo or regular bronchodilator therapy (2-4,7), 4 mg nedocromil sodium given twice

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Table 1 Details of double-blind, controlled studies in adults of the use of 4 mg nedocromil sodium administered via metered dose inhaler

Reference	Nedocromil sodium (daily dose)	Weeks of treatment	Number of patients
1	4 mg × 2	8	112
2	4 mg × 4	10	10
3	4 mg × 2	8	35
4	4 mg × 4	2 × 6	29
5	4 mg × 4	12	212
6	4 mg × 2	52	263
	4 mg × 4		456
7	4 mg × 2	3 × 4	76
	4 mg × 4		
8	4 mg × 4	2 × 8	28
9	4 mg × 4	22	69
10		Meta-analysis	

Table 2 Details of large-scale, placebo-controlled studies in children of the use of nedocromil sodium administered via metered dose inhaler

Reference	Nedocromil sodium (daily dose)	Weeks of treatment	Number of patients	Age range (years)
11	4 mg × 4	12	209	6–17
12	4 mg × 3	8	120	6–19
13	4 mg × 4	8	134	6–12
14	4 mg × 4	12	234	6–11
15	4 mg × 4	2 × 6	90	3–12
16	4 mg × 2	6	120	6–12
	5 mg × 4 (Intal)			
17	4 mg × 4	6	12	7–17
18	4 mg × 3	16	15	—
19		Review		
20		Review		
21	4 mg × 4	52	65	3–11

(3,7) or four times a day (2,4,7) significantly improved mean daily peak expiratory flow, concurrent with significant reductions in concomitant bronchodilator use. Significant improvements in diurnal variation in peak flow (4,5) and in bronchial hyper-responsiveness have also been demonstrated (4). These changes (4,5) were apparent during the first period of assessment.

In the period since the publication of the BTS Guidelines, a meta-analysis of all double-blind, placebo-controlled clinical trials supplied and analysed by Fisons (irrespective of positive or negative outcome or publication status) has been carried out (10). It is believed that, at the time of the analysis, no other source of inhaled nedocromil sodium and matching placebo was available, hence the analysis included all clinical trials – the only restriction being the exclusion of studies with less than nine patients per treatment group. Efficacy data from 4723 patients (2385, nedocromil sodium; 2338, placebo) were analysed by dose (4 mg twice or four times a day), by trial design and overall, and were presented as the difference (with 95% confidence limits) between nedocromil sodium and placebo of the change from baseline for day and night asthma, cough, peak expiratory flow rate, FEV_1, inhaled bronchodilator use, and percent of patients reporting a very or moderately effective therapy. Overall, the analysis showed a highly significant effect of nedocromil sodium compared with placebo, for the two doses and for all efficacy variables. It was clear, however, that the clinical improvement with nedocromil sodium was greatest in the mild to moderate asthmatic patients maintained on bronchodilator therapy.

Nedocromil Sodium and Children

Six large-scale, placebo-controlled studies of the use of nedocromil sodium administered *via* MDI in children have been published since the first BTS Guidelines review (11–16) (see Table 2). Two studies have been published in full (11,12), and the remainder have been published as abstracts (13–16). The ages of the treated children ranged from 3 to 19 years.

Addition of 4 mg nedocromil sodium or placebo four times daily to the predominantly bronchodilator therapy of extrinsic asthmatic children (11), led to significant improvements in total symptom score and daily inhaled bronchodilator use in the nedocromil-sodium-treated patients; symptom severity and bronchodilator use were halved in the nedocromil-sodium-treated children compared with negligible reductions in placebo-treated children. Similar results were apparent in an 8-week in-season study of ragweed-sensitive children also randomized to receive 4 mg nedocromil sodium or placebo four times a day, with significant improvements in total symptom score, daytime asthma, morning asthma, daytime cough, sleep disturbance and salbutamol bronchodilator use (13).

Mild, episodic asthmatic children currently receiving bronchodilator therapy had a significantly greater

percentage of symptom-free days, and significantly reduced total symptom (evident from the first period of assessment) and cough scores when treated with 4 mg nedocromil sodium four times daily compared with placebo, despite the study taking place during a time of anticipated exposure to environmental triggers (14). In 90 asthmatic children who were either newly diagnosed or taking only bronchodilators as necessary, 4 mg nedocromil sodium four times a day delivered *via* a holding chamber device was again significantly more effective (total symptoms, daytime symptoms, percentage of symptom-free days, and percentage of days using a β_2-bronchodilator) than placebo (15). Interestingly, children previously well-controlled on 15–40 mg sodium cromoglycate daily did not deteriorate when randomized to either 4 mg nedocromil sodium twice daily or 5 mg sodium cromoglycate four times daily, and showed no significant differences between treatment groups, suggesting a potential compliance advantage for nedocromil sodium (16).

In placebo comparisons, when added to the current therapy of stable, mildly asthmatic children, 4 mg nedocromil sodium three times daily led to significant improvements in FEV_1 and FVC, and a greater proportion of the children attaining normal lung function (12), whilst a four times daily dose produced significant improvements in daily peak expiratory flow, concurrent with a significant reduction in daily bronchodilator use (11). Bronchial responsiveness to histamine did not differ between groups in the former study (12), whereas two smaller studies showed 4 mg nedocromil sodium taken either three or four times daily significantly reduces non-specific bronchial responsiveness to ultrasonically nebulized distilled water and methacholine (17,18).

A recent summary of the human safety data on nedocromil sodium indicated that it has an excellent safety profile, is well tolerated and that adverse events are generally mild (19). From the data then available (20), it was considered that nedocromil sodium was also well tolerated in children. Since then, data from an open, long-term safety study in 65 chronic asthmatic children (21) who received 4 mg nedocromil sodium four times a day for 1 yr have shown excellent acceptability (fair-to-excellent in 92%), with no withdrawals as a result of treatment, and an incidence and type of adverse event that was unremarkable (e.g. headache, cough and pharyngitis). These data are supportive of the findings from the individual clinical trials, and demonstrate that nedocromil sodium is well tolerated in children.

Anti-inflammatory Activity of Nedocromil Sodium

The anti-inflammatory activity of nedocromil sodium has been confirmed in man *in vitro* (20,22–24). Current pre-clinical research suggests that nedocromil sodium may act through an effect on chloride channels (25). Data published since the BTS Guidelines have confirmed an anti-inflammatory activity for nedocromil sodium *in vivo* in man, derived from clinical pharmacologic and therapeutic studies. To date, no studies of the anti-inflammatory activity of nedocromil sodium have been carried out *in vivo* in children. Recent research suggests, however, that wheezing in children and asthma in adults may have common cellular mechanisms (26).

Nedocromil sodium has been shown to inhibit the late asthmatic response when given before (27) and after the early response (28). Therefore, nedocromil sodium may affect this inflammatory response model of the airways irrespective of any mast-cell-driven effects. Nedocromil sodium inhibited the 48-h post-challenge infiltration of eosinophils into bronchoalveolar lavage (BAL) fluid of ragweed-allergic subjects (29), and restored post-challenge peripheral blood circulating eosinophil and basophil cell numbers towards normal (27).

Bronchoalveolar lavage fluid eosinophil, neutrophil and lymphocyte numbers, BAL fluid inflammatory mediators and peripheral blood circulating eosinophil cell numbers were significantly reduced in adult atopic asthmatics after receiving 4 mg nedocromil sodium four times daily for 17 weeks (30). These findings were concurrent with significant improvements in cough, dyspnoea and sleep difficulty, and non-specific bronchial responsiveness to ultrasonically nebulized distilled water. In two similar, controlled, four times daily dosing studies [a 12-week placebo comparison (31) and a 16-week comparison with 200 μg salbutamol (32)], significant increases in morning and evening peak expiratory flow, and night-time bronchodilator use were preceded by and concurrent with significantly reduced plasma protein leakage (31). Total and activated eosinophil numbers from bronchial biopsy increased in the salbutamol-treated patients and decreased in the nedocromil-sodium-treated patients, such that the between-active treatment differences were significant (32).

Conclusion

The clinical trials and clinical research data support the conclusion that nedocromil sodium has an anti-inflammatory activity and, at a dose of 4 mg two

to four times daily, will be effective in the treatment of mild to moderate asthma in adults and children.

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