NSAIDs in the treatment of adult asthma: Sodium cromoglycate and nedocromil sodium

MICHEL-Y ROULEAU MD
Service de pneumologie et d'allergie, Hôpital du Saint-Sacrement, Québec, Québec

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Among nonsteroidal anti-inflammatory drugs used in the treatment of adult asthma, sodium cromoglycate and nedocromil sodium are the most frequently prescribed. These medications have a similar efficacy profile in asthma although it has been suggested that nedocromil is more powerful than cromoglycate, particularly in its steroid sparing effects. Both drugs have been recommended as alternatives to steroids in the treatment of mild asthma. They are useful in the prevention of bronchospasm induced by exposure to allergens or to a variety of other stimuli. In comparison with theophylline or low dose inhaled steroids, cromoglycate and nedocromil have shown a similar antiasthmatic efficacy, although this is variable among patients.

Key Words: *Asthma, Nedocromil sodium, Nonsteroidal anti-inflammatory drugs, Sodium cromoglycate*

Les médicaments anti-inflammatoires non stéroïdiens dans le traitement de l'asthme de l'adulte : le cromoglycate de sodium et le nédocromil de sodium

RÉSUMÉ : Parmi les médicaments anti-inflammatoires non stéroïdiens utilisés pour traiter l'asthme de l'adulte, les plus fréquemment prescrits sont le cromoglycate de sodium et le nédocromil de sodium. Ces agents ont un profil d'efficacité similaires dans l'asthme bien qu'il semble que le nédocromil soit plus puissant que le cromoglycate, particulièrement dans ses effets d'épargne de stéroïdes. Ces deux médicaments ont été recommandés comme autres possibilités de traitement de l'asthme léger en remplacement des stéroïdes. Ils sont utiles pour prévenir le bronchospasme induit par l'exposition aux allergènes ou par une variété d'autres stimuli. Comparativement à la théophylline ou aux stéroïdes en inhalation à faible dose, le cromoglycate et le nédocromil ont démontré une efficacité anti-asthmatique similaire. Cependant, ces résultats varient selon les patients.

SODIUM CROMOGLYCATE AND NEDOCROMIL SODIUM ARE two medications currently used in the treatment of asthma. Cromoglycate has been available for more than 20 years, and nedocromil sodium for a shorter while. The antiasthmatic effect of these medications is presumed to be due to their anti-inflammatory properties, since neither one has a bronchodilator effect (1). It was initially believed that cromoglycate had an antiasthmatic effect principally from inhibition of the release of mediators by mast cells. It is now evident that the two medications have a vast spectrum of anti-inflammatory effects in vitro and in animal models in vivo.

Other agents are considered to have antiallergic or anti-inflammatory properties: they include ketotifen, whose clini-

Correspondence and reprints: Dr Michel-Y Rouleau, Hôpital du Saint-Sacrement, 1050, chemin Sainte-Foy, Québec, Québec G1S 4L8. Telephone (418) 682-7918, Fax (418) 682-7728

cal indication is principally limited to the treatment of asthma in children, and some immunomodulators such as methotrexate, which is rarely used because of its toxicity. They are not included in this discussion.

SODIUM CROMOGLYCATE

Sodium cromoglycate was discovered in the 1950s during research on a natural antispasmodic, khellin. This furanochromone is derived from a Mediterranean plant called *Ammi visnaga* (Umbelliferae), whose seeds had been used as a smooth muscle relaxant since ancient times. It was observed that the derivatives of khellin, in which the methyl group is replaced by a carboxylic acid group, did not have bronchodilator properties but inhibited the bronchoconstriction provoked by inhalation of an allergen (2). These promising results were confirmed by clinical studies, and led to the development of sodium cromoglycate (also called cromolyn sodium), which was made available in Great Britain in 1968 and in North America in the '70s.

Mechanism of action

The precise mode of action of cromolyn has not yet been completely identified. It has been suggested that its principal mechanism of action is the stabilization of mast cells (3) through inhibition of their degranulation (4). Cromolyn also inhibits the activity of other cells such as peripheral white blood cells, monocytes and platelet activating factor (5,6). In vitro, cromolyn alleviates the bronchoconstriction caused by acetylcholine, histamine, serotonin, bradykinin and prostaglandin $F_{2\alpha}$. It has also been shown that cromolyn inhibits bronchoconstriction induced in asthmatic subjects by nonimmunological stimulants such as exercise (7,8).

In a canine model, cromolyn inhibited the response of the 'C fibre' nerve endings, which initiate the bronchoconstrictor reflex (9). It also inhibited bronchoconstriction induced by leukotriene D4 (10).

Clinical pharmacology

Sodium cromoglycate has been reported to prevent bronchospasm induced by a variety of physical stimuli, such as exercise, cold air, fog and hyperventilation, if it is administered before exposure (11,12). Cromolyn is also known to inhibit bronchospasm induced by sulphur dioxide, toluene diisocyanate and adenosine, although this effect seems to be variable and dose-dependent (7,13). During allergen bronchoprovocation, administration of a single dose of cromolyn or nedocromil beforehand can reduce both the (early) immediate and the late asthmatic response (14). Cromolyn, nedocromil and steroids, but not $beta_2$-agonists, provide significant protection against the increase in bronchial responsiveness produced by an allergen (15,16).

When administered after a specific bronchial provocation and approximately 1 h before the late reaction, cromolyn will delay the beginning of the reaction and diminish its length but it will not significantly modify the magnitude (17). A reduction in nonspecific bronchial hyperreactivity has been noted in patients during natural allergen exposure in sensitized asthmatic subjects when cromoglycate was used (18). A reduction in the eosinophil count of bronchoalveolar lavage in patients treated with cromolyn was observed in those who had demonstrated a clinical improvement, but not in those who had not (19).

Therapeutic efficacy

In the majority of studies, cromoglycate improved asthma in 60 to 80% of patients (20-23). In double-blind studies, cromolyn was usually significantly superior to placebo in controlling asthma symptoms and in reducing the concomitant bronchodilator medication. Peak expiratory flow in the groups using cromolyn was often significantly superior to the placebo group.

In the treatment of mild to moderate chronic asthma, cromolyn and theophylline have comparable short term efficacy, although theophylline is frequently associated with gastrointestinal and central nervous system-related side effects (24-28). Using both medications together results in an additive effect in the control of asthma symptoms.

Cromolyn inhibits bronchospasm caused by exercise and hyperosmolar solutions when used beforehand, but it is less effective than $beta_2$-agonists (29,30). When used concomitantly with $beta_2$-agonists, cromolyn produces an additional preventive effect against exercise-induced bronchospasm.

Sodium cromoglycate has been evaluated in relation to corticosteroid use. Some preliminary studies have suggested that doses of corticosteroids could be reduced in some patients by addition of cromolyn.

In 1973, Friday et al (31) found that of 18 corticosteroid-dependent patients who had completed one year of cromolyn therapy, seven could stop taking corticosteroids and the dosage could be diminished in 10, while it was increased in one. Toogood et al (32) studied 30 patients controlled by high doses of inhaled beclomethasone diproprionate (mean of 1040 mg daily) and found no advantage to adding cromolyn in comparison with a placebo, suggesting that cromolyn had no significant inhaled steroid-sparing effect. Other clinical trials have not demonstrated any additional benefits of combined therapy (cromolyn and corticosteroids), indicating that the 'steroid-sparing effect' of cromolyn may not be as pronounced as was initially suggested (33).

NEDOCROMIL SODIUM

Nedocromil is a relatively new pyranoquinoline with a similar spectrum of action to that of cromolyn, but which seems to have superior anti-inflammatory properties.

Pharmacokinetic properties

Because nedocromil is highly soluble in water, it is rapidly absorbed by porous tissues such as the lungs, but hardly absorbed by tissues such as the gastrointestinal tract. There is little systemic absorption and most of the medication is excreted in the stools (34). Because protein binding is moderate to low, there are no interactions due to drug displacement. It is rapidly excreted unchanged in the urine and the bile. This medication interferes little with the metabolic processes, and

its clearance is rapid. Because it does not cross the placental and blood-brain barriers and there is little accumulation in the organism, it is very safe (35).

Pharmacology

Nedocromil sodium inhibits in vitro neutrophil-induced chemotaxis (36), exocytosis of leukotriene C_4 by eosinophils (37), activation of macrophages and monocytes by immunoglobulin E (38), release of histamine by mast cells (39) and cytotoxicity of platelets (40).

In vivo studies of animal models showed that nedocromil blocked the early bronchoconstriction caused by inhalation of an antigen (40) and adenosine (41); it inhibited the increase in vascular permeability induced by ovalbumin (42) and could also block the late asthmatic reaction and increases in bronchial reactivity (43). When nedocromil sodium was compared with cromolyn in models involving mast cells, eosinophils and neural stimulants, nedocromil sodium proved to be more powerful.

Clinical pharmacology

Several clinical pharmacology studies using a single 4 mg or 8 mg dose of nedocromil sodium showed that it protected against bronchospasm provoked by inhalation of allergens (44,45) and physical stimuli such as exercise (46), cold air (47) and fog (48), probably by its effect on the degranulation of mast cells.

Nedocromil has also been shown to be effective in inhibiting bronchoconstriction induced by inhalation of adenosine monophosphate (49), inhalation of sulphur dioxide (50), sodium metabisulphite (51), bradykinin (52), substance P (53) and neurokinin A (54) secreted by sensory afferent nerves in the lungs. The underlying mechanism seems to be related to the degranulation of the mast cells; nedocromil and cromolyn have a similar profile of action, although nedocromil is more potent.

In challenges involving inflammatory or neuronal pathways, nedocromil appears to be more efficient than cromolyn and therefore may be working via a different mechanism.

In a number of studies involving allergen challenges (55,56), nedocromil has been shown to prevent late asthmatic reactions when the medication is given in a single dose beforehand. It has been reported (57) that nedocromil administered in three doses over a 1 h period before the late reaction prevented it, even when nedocromil was not administered beforehand. Nedocromil also seems to have an effect on the bronchial hyperreactivity induced by inhalation of an allergen (57).

Therapeutic efficacy

Comparison with placebo as an addition to existing therapy: When nedocromil sodium is added to current treatment, it is more effective than a placebo in reducing the symptoms of asthma and $beta_2$-agonist need. Nedocromil improved pulmonary function and was preferred to placebo as assessed by both physicians and patients in most of the trials. Several studies (58-60) showed significant differences between nedocromil sodium and placebo in most of the variables assessed; others (61-63) showed significant differences in only some of the criteria assessed. Compared with placebo, nedocromil sodium also produced an improvement in the symptoms and peak flow measurements of patients already on a maintenance dose of inhaled steroids (59,62). The differences between the nedocromil and placebo groups were, however, inconsistent and small, although statistically significant.

Therapeutic efficacy as replacement therapy for maintenance bronchodilator: When nedocromil sodium is compared with placebo in well-controlled trials as a replacement of maintenance bronchodilator medication, either a methylxanthine (60,64) or inhaled $beta_2$-agonist (65), the results favour nedocromil sodium, 8 or 16 mg a day, over placebo.

Therapeutic efficacy as replacement therapy for corticosteroids: Boulet et al (66) reported a decrease in the oral corticosteroid dosage of patients treated with nedocromil compared with those who received a placebo. Although Goldin and Bateman (67) could not show this same effect, in the study by Boulet et al, patients were treated with nedocromil sodium for a longer period before reduction of the oral dose of corticosteroids.

In patients taking inhaled but not oral corticosteroids, studies by Bone et al (68), where the dosage of inhaled corticosteroids was reduced by half before the beginning of the study, and by Greif et al (69), where the inhaled corticosteroids were stopped two weeks before the beginning of the study, showed a superior control of asthma symptoms in the nedocromil-treated group over those taking placebo. In a group of patients on high doses of inhaled corticosteroids (beclomethasone 1000 or 2000 µg a day), the addition of nedocromil resulted in only a minor reduction in the dosage of corticosteroids globally compared with placebo, although the degree of reduction was variable (70). Nedocromil sodium seems to lead to a modest reduction in the dosage of corticosteroids required to control asthma, but this varies among patients.

Comparative studies with bronchodilators: In a study using ipratropium as a rescue medication, 4 mg of nedocromil qid was compared with 200 µg of salbutamol qid. The results favoured the treatment with nedocromil (71).

Johnson and Lloyd (72) in a multicentre nonblinded study compared the efficacy of nedocromil 4 mg qid with salmeterol 50 µg bid in patients with mild asthma. After six weeks, peak expiratory flow and the control of symptoms showed an improvement that was more significant with salmeterol than with nedocromil sodium.

A study (73) comparing a daily dose of theophylline designed to maintain the plasma concentration between 10 and 20 mg/L with nedocromil sodium 4 mg qid showed no difference between the two groups after eight weeks of treatment.

Comparison with cromolyn: Nedocromil sodium 4 mg qid daily was shown to be more effective than cromolyn sodium 10 mg four times daily in reducing the symptoms of asthma (74). In an another study (75) on patients well controlled with low or moderate doses of corticosteroids, this medication was

progressively reduced until symptoms reappeared; the addition of nedocromil to their treatment was shown to be more effective than cromolyn. No differences were noted between nedocromil and cromolyn in therapeutic efficacy of a group of asthma patients over 50 years of age (76). Nedocromil has also been shown to have some protective effects on exercise-induced asthma (77) that seem superior to cromolyn (78).

Comparison with inhaled corticosteroids: Several studies actually seem to demonstrate that the use of nedocromil sodium 4 mg qid and beclomethasone diproprionate 100 µg qid are of approximately equal efficacy when added to a maintenance therapy with bronchodilators (79-82), although one study showed a better control of symptoms with beclomethasone (80). However, nedocromil 4 mg bid seems to be less effective than beclomethasone diproprionate 200 µg bid (82).

Dosage, administration and tolerance

In Canada, nedocromil sodium is available as a metered dose inhaler (2 mg per inhalation). The usual recommended dose in the treatment of asthma in adult patients and children 12 years and up is 4 mg two to four times daily. Nedocromil is not a bronchodilator and should not be used to control acute asthma attacks. It should be used for regular maintenance treatment. The secondary effects most often reported are an unpleasant taste, cough, sore throat and headache.

CONCLUSION

Where should we position nedocromil in the therapeutic approach to adult asthma?

Nedocromil sodium has been shown to be effective in mild to moderate asthma. An international consensus report on the diagnosis and management of asthma (83) recommends a choice of three first-line anti-inflammatory agents: 200 to 500 µg of inhaled steroids, sodium cromoglycate, and nedocromil sodium as maintenance therapy in mild to moderate asthma when beta$_2$-agonists are used more than three times a week. A meta-analysis recently concluded that nedocromil could be used as a first-line treatment in the maintenance of patients with mild to moderate asthma (84). O'Byrne and Cook (85) in an editorial proposed that the meta-analysis did not supply sufficient information on tolerance and relative efficacy compared with the actual treatments (such as with cromoglycate or low doses of inhaled corticosteroid) suggested as the first-line approach for patients diagnosed as mild to moderate asthmatics. They argued that the information is still weak for nedocromil, and without it, it is difficult to decide on the appropriate use of nedocromil in the treatment of asthma.

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