Nonsteroidal anti-inflammatory agents in the treatment of asthma in children

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The increasing scientific information clearly demonstrates the importance of inflammation in asthma. This evidence has led physicians to focus their treatment on the elimination of inflammation instead of working solely against bronchoconstriction. Steroids and nonsteroidal agents are currently used to prevent this inflammatory component. This paper focuses only on nonsteroidal anti-inflammatory agents such as sodium cromoglycate, nedocromil sodium and ketotifen and their use in pediatric asthma. The discussion on each medication addresses its mechanism of action, the evidence concerning its efficacy in pediatrics (i.e., clinical pharmacology, acute bronchial challenge, late asthmatic response, bronchial hyperreactivity, clinical efficacy) and the pediatric dose.

Key Words: Asthma, Children, Nonsteroidal anti-inflammatory agents

SODIUM CROMOGLYCATE

Sodium cromoglycate was introduced in England for the treatment of asthma in 1968. It is a derivative of khellin, a furocoumarin obtained from the Mediterranean plant Ammi visnaga (Umbrillferae). In folk medicine, the seeds of this plant were used for their smooth muscle relaxant properties. Khellin derivatives in which the 2-methyl group has been replaced by a carboxylic acid moiety, as in sodium cromoglycate, have no bronchodilating properties; however, they can inhibit bronchoconstriction induced by inhalation challenge with antigen (1). Sodium cromoglycate is a white hydrated powder, highly polar, with a pKa of 2 and a molecular weight of about 500 Da. It can be administered from three different formulations: dry powder, solution for nebulization or metered dose inhaler.

Mechanism of action

The precise mechanism of action of sodium cromoglycate has not been completely elucidated. One of its primary modes of action is thought to be the stabilization of mast cells, which
prevents the subsequent release of mediators. Sodium cromoglycate inhibits mast cell degranulation produced by immunoglobulin E antibody reactions, phospholipase A, compound 48/80, and the calcium ionophore A23187 (2–4). This mast cell membrane stabilization appears to be related to the phosphorylation of a membrane protein that can modulate calcium intracellular influx (5). Other modes of action include the reduction of bronchoconstriction by an action on the different arms of the nervous reflexes and the reduction in the activity of lung irritant receptors and the inhibition of C fibre nerve endings (6).

The increasing emphasis on the inflammatory component of asthma obstruction and its relationship with bronchial hyperreactivity has led to the study of sodium cromoglycate in models involving inflammatory cells. The administration of sodium cromoglycate can prevent the activation of peripheral blood neutrophils and eosinophils following immunological and nonimmunological stimuli (7,8). Others have shown that its prolonged administration has resulted in a significant decrease of eosinophils in bronchoalveolar lavage fluids (9). This potential of sodium cromoglycate to reduce inflammation may be more important than its mast cell stabi
ing in regard to its antiallergic effect.

Sodium cromoglycate has no intrinsic bronchodilator properties. In vitro, it reduces the contraction of smooth muscle induced by acetylcholine, histamine, serotonin, bradykinin, and prostaglandin (PG) E₂. Furthermore, it potentiates smooth muscle relaxation induced by isoproterenol, adrenaline, PGF₁α; and salbutamol (11). In vivo, sodium cromoglycate inhibits bronchoconstriction produced by exercise, the inhalation of cold air, sulphur dioxide, the nebulization of distilled water and leukotriene D₄ (6,10–15).

Clinical pharmacology

Acute bronchial challenge: The administration of sodium cromoglycate can prevent the immediate and late asthmatic response to antigen challenge. Allunyan (16) demonstrated that the administration of sodium cromoglycate before an antigen challenge inhibited the fall in forced expiratory volume in 1 s (FEV₁). This protective effect diminished, how
ever, when sodium cromoglycate was given after the antigen challenge. Furthermore, this protective effect of sodium cromoglycate lessened when the time between its inhalation and antigen challenge was increased (16). Although results on sodium cromoglycate’s protective effect against constricting agents such as methacholine and histamine are conflicting (1), most studies have demonstrated its efficacy against numer
ous bronchoconstricting agents such as carbachol, sulphur dioxide, and cold air (3).

Late asthmatic response: Many asthmatics undergo a second bronchoconstrictive response 4 to 12 h following inhalation challenge with antigen. This phenomenon is known as the delayed or late asthmatic response. Sodium cromoglycate also blocks this late asthmatic response when given before challenge with a variety of antigens. Since the late asthmatic response is associated with severe asthma and correlates with increased bronchial hyperreactivity, some authors feel that the role of sodium cromoglycate in preventing this late reaction may be one of the keys to its ability to control and improve chronic asthma.

Bronchial hyperreactivity: Airway hyperreactivity is a characteristic feature of asthma and the degree of bronchial responsiveness, as measured by histamine challenge, has been shown to correlate with the severity of asthma. Despite some conflicting results, most studies have demonstrated that long term administration of sodium cromoglycate can reduce bronchial hyperreactivity in both adults and children (17). The results of several pediatric studies are presented in Table 1.

Clinical efficacy: Several studies have investigated the efficacy of sodium cromoglycate in the treatment of asthma (18). In pediatric studies, sodium cromoglycate was shown to be superior to placebo in improving pulmonary function tests and in reducing asthmatic symptoms. Physician assessed asthma severity and concomitant bronchodilator use (beta-agonists and theophylline) (18–20). The amount of sodium cromoglycate deposited in the lung and subsequently absorbed depends upon the dose administered, the delivery system and the proper technique. There is no direct correla
tion, however, between clinical efficacy and either the amount of drug deposited in the lung or cromolyn blood concentration (1).

<table>
<thead>
<tr>
<th>Authors (reference)</th>
<th>n</th>
<th>Age (years)</th>
<th>Severity</th>
<th>Delivery system</th>
<th>Duration</th>
<th>Challenge</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dickens 1970</td>
<td>17</td>
<td>0–16</td>
<td>Severe</td>
<td>Spincaps</td>
<td>2 weeks</td>
<td>Exercise</td>
<td>+</td>
</tr>
<tr>
<td>Dickens 1979</td>
<td>17</td>
<td>3–16</td>
<td>Severe</td>
<td>Spincaps</td>
<td>10 years</td>
<td>Histamine</td>
<td>+</td>
</tr>
<tr>
<td>Furukawa et al 1984</td>
<td>85</td>
<td>5–15</td>
<td>Mild/moderate</td>
<td>Spincaps</td>
<td>12 weeks</td>
<td>Methacholine</td>
<td>+</td>
</tr>
<tr>
<td>Kramer et al 1984</td>
<td>85</td>
<td>5–17</td>
<td>Mild/moderate</td>
<td>Nebuliser</td>
<td>6 weeks</td>
<td>Carbachol</td>
<td>+</td>
</tr>
<tr>
<td>Shapiro et al 1988</td>
<td>87</td>
<td>6–12</td>
<td>Mild/moderate</td>
<td>Nebuliser</td>
<td>8 weeks</td>
<td>Histamine</td>
<td>+</td>
</tr>
<tr>
<td>Watanabe 1988</td>
<td>17</td>
<td>6–16</td>
<td>Moderate/severe</td>
<td>Spincaps</td>
<td>3 years</td>
<td>Histamine</td>
<td>+</td>
</tr>
</tbody>
</table>

Data adapted from reference 17. *Cited in reference 17. + Decrease effect; – No effect

TABLE 1
Sodium cromoglycate 20 mg qid effect on lung hyperreactivity in children
Sodium cromoglycate has also been compared with other medications such as theophylline and steroids in the treatment of asthma. Some of the comparative studies between sodium cromoglycate and theophylline that were performed in children are summarized in Table 2 (1).

These studies clearly demonstrate that sodium cromoglycate and theophylline are equally efficacious in the control of asthma symptoms and in improving pulmonary function tests; however, theophylline caused more gastrointestinal and central nervous system side effects. In addition, sodium cromoglycate has an advantage over theophylline for long term use because of its ability to decrease bronchial hyperreactivity.

Both theophylline and sodium cromoglycate inhibit exercise-induced asthma but are less efficacious than betaglycylnergic agents. Sodium cromoglycate should be selected over these agents if a patient requires their use more than two to three times a week.

Early clinical studies of steroid dependent asthmatic patients suggested that the addition of sodium cromoglycate could have a corticosteroid sparing effect (21, 22). More recent data, however, could not confirm these results and were not able to demonstrate any benefit from combined sodium cromoglycate and corticosteroid therapy (23-25). Based on these results, there appears to be no advantage in prescribing sodium cromoglycate to steroid dependent patients.

Pediatric dose
Sodium cromoglycate is available in Canada in three forms - 20 mg powdered capsule delivered via the Spinhaler (Fisons) apparatus, 1% solution containing 20 mg of sodium cromoglycate per 2 mL of distilled water delivered by a compressor-driven nebulizer, and a pressurized metered-dose inhaler that releases 1 mg per actuation.

No pediatric study has been done to evaluate a possible dose-response effect for sodium cromoglycate; those carried out only compared single doses administered with different apparatus. In one study (26), 2 mg doses of sodium cromoglycate administered via metered dose inhaler and 20 mg administered via a Spinhaler apparatus were both efficacious in preventing exercise-induced asthma. In another study (27), doses of 2 mg sodium cromoglycate administered qid via a metered dose inhaler and 20 mg administered qid via a Spinhaler apparatus were equally efficacious in controlling chronic asthma symptoms. Carello and a metered (28) noted, however, that although beneficial effects of sodium cromoglycate were equivalent at the end of the study period, they appeared sooner in patients receiving 10 mg qid via metered dose inhaler instead of 2 mg qid via metered dose inhaler.

Results from adult studies on dose-response effects are conflicting (17). Differences noted in adults can be partially explained by the fact that a dose-response effect seems to depend on the type of stimuli used to induce bronchospasm. For example, Tulfet et al (29) demonstrated that 20 mg of sodium cromoglycate administered with a metered dose inhaler was more efficacious than 2 mg to prevent exercise-induced asthma. In contrast, Latimer et al (30) noted that doses of 2, 10 and 20 mg all administered via a metered dose inhaler offered a protection against bronchoconstriction following inhalation of cold air similar to the one obtained with 20 mg of sodium cromoglycate given with a Spinhaler.

Some authors have demonstrated that the duration of the effect of sodium cromoglycate is partially related to the amount given and the type of challenge stimulus used. Patel and Kerr (31) noted that doses of 20 mg and 40 mg of sodium cromoglycate continued to provide a partial protection against an exercise-induced fall in FEV1 270 mins after their administration, whereas the effect of 2 mg had worn off.

Several clinicians feel that the European formulation of 5 mg of sodium cromoglycate delivered by a metered dose inhaler is more efficacious that the 1 mg available in North America. There are no pediatric studies, however, to support that contention.

Sodium cromoglycate is very safe. The median parental lethal dose for different animal species is 4000 mg/kg (1). The inhalation route is even safer (1). Indeed, numerous studies involving mammals could not achieve lethal doses of sodium cromoglycate. Sodium cromoglycate produces no ill effect on normal immunological reactions, mucociliary activity or lung surface active properties and has no mutagenic or teratogenic effect. Side effects from sodium cromoglycate are rare.

Based on data available in the literature, most patients should be adequately treated with the recommended dose of

<table>
<thead>
<tr>
<th>Authors (reference)</th>
<th>N</th>
<th>Age (years)</th>
<th>Symptom control</th>
<th>PFT Improvement</th>
<th>Bronchodilators pm</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hambleton et al 1977 (80)</td>
<td>28</td>
<td>Children</td>
<td>C = T = (G+T)</td>
<td>C = T = (G+T)</td>
<td>C = T = (G+T)</td>
<td></td>
</tr>
<tr>
<td>Edmonds et al 1980 (89)</td>
<td>30</td>
<td>5-15</td>
<td>P = T = C</td>
<td>P = T = C</td>
<td>P = T = C</td>
<td>P = T = C</td>
</tr>
<tr>
<td>Glass et al 1981 (90)</td>
<td>16</td>
<td>2-4</td>
<td>P = T = C</td>
<td>P = T = C</td>
<td>P = T = C</td>
<td>P = T = C</td>
</tr>
<tr>
<td>Newth et al 1982 (91)</td>
<td>26</td>
<td>1-6</td>
<td>T = (G+T)</td>
<td>T = (G+T)</td>
<td>T = (G+T)</td>
<td>T = (G+T)</td>
</tr>
<tr>
<td>Finkebusch et al 1984 (92)</td>
<td>46</td>
<td>6-15</td>
<td>B = T = G</td>
<td>B = T = G</td>
<td>B = T = G</td>
<td>B = T = G</td>
</tr>
<tr>
<td>Springer et al 1985 (93)</td>
<td>13</td>
<td>8-13</td>
<td>T = C = G</td>
<td>T = C = G</td>
<td>T = C = G</td>
<td>T = C = G</td>
</tr>
</tbody>
</table>

Data adapted from reference 1 - as not as effective: B Baseline, C Cromoglycine sodium: ND No difference: P Placebo; PFT Pulmonary function tests; pm Used as required; T Theophylline

TABLE 2
Sodium cromoglycate versus theophylline

Data from reference 1.
NEDOCROMIL SODIUM

Nedocromil sodium is the disodium salt of a pyranopyrimidine dicarbonyl acid (32). Nedocromil sodium is a pale yellow powder, hydrophilic with a molecular weight of 415. Following inhalation of nedocromil sodium in healthy volunteers, plasma concentrations rise rapidly and reach peak levels reached in 20 mins, whereupon they plateau for 1 h followed by a decline in plasma levels. These plasma levels suggest the persistence of nedocromil in the lungs for a longer period than would be expected and may account for therapeutic efficacy with a twice daily regimen (33).

Mechanism of action

Nedocromil sodium is a cromolyn-like agent with anti-allergic and anti-inflammatory properties. In animals, nedocromil sodium was able to inhibit partially bronchoconstriction induced by bradykinin, which is partially related to an inhibition of the ars1 and other specific antigens as seen in the ascaris-sensitive Macaque species monkey (34).

In vitro studies have shown that nedocromil sodium is a more potent inhibitor than sodium cromoglicate in the release of histamine, leukotriene C4 and prostaglandin D2 in primate lung mast cells, and of histamine in human mast cells (35-36). It can also prevent chemotactic and inflammatory mediator release from animal derived effector cells such as granulocytes, monocytes, macrophages, eosinophils, platelets and mast cells (37-38).

Clinical pharmacology

Acute and late bronchial challenge: Results from numerous adult studies have demonstrated that nedocromil can prevent bronchoconstriction induced by exercise, fog, cold air, adenovirus, sodium cromoglicate and agents (32,39-42). Moreover, it was also more efficacious than sodium cromoglicate in these studies. In pediatrics there is a paucity of such studies. However, the few studies conducted on this subject demonstrate that nedocromil was also able to prevent exercise-induced asthma in children (Table 3) (32,43-46). In one pediatric study where nedocromil sodium efficacy in the prevention of exercise-induced asthma was compared with sodium cromoglicate efficacy, both treatments produced a similar response (46). Similar to sodium cromoglicate, nedocromil sodium can inhibit the late bronchoconstrictor response to allergen challenge (47). Bronchial hyperreactivity: Airway hyperreactivity commonly occurs following antigen exposure during the pollen season. Studies in adults have shown that nedocromil sodium can significantly decrease bronchial hyperreactivity (48-49).

Mechanism of action: Numerous studies in adults have investigated the efficacy of nedocromil sodium in the treatment of asthma. Recently, Edwards and Stevens (50) published a meta-analysis of all known placebo controlled, double-blind, randomized therapeutic trials. Overall, their meta-analysis demonstrated that nedocromil sodium decreased the use of inhaled bronchodilators, reduced day- and nighttime symptoms of asthma and improved pulmonary function tests such as mean daily peak expiratory flow rate and FEV1 (50).

Preliminary studies in children reported an improvement in lung function and a decrease in bronchodilator requirements during the administration of nedocromil sodium (32,38). Studies in adults on the steroid sparing effect of nedocromil have generated conflicting data (51-54). Such data are not available in pediatrics.

In vitro and adult studies suggest that nedocromil sodium is a more potent anti-inflammatory and antiasthmatic agent than sodium cromoglicate (32,35,36,39-42). There are no data in the pediatric literature to confirm or refute this conclusion. In the absence of this information it is difficult to determine the exact role and place of nedocromil sodium in the treatment of asthma in children.

Pediatric dose

Nedocromil sodium is only available in a metered dose inhaler formulation. There is no dose-response effect for nedocromil sodium in children. The recommended dose is 4 mg qid. When the patient is stabilized, this dose can be tapered to bid (32).

KETOTIFEN

Ketotifen is a benzocycloheptanophenone derivative with antihistaminic and antiinflammatory properties. Ketotifen is rapidly absorbed following oral administration, and peak plasma levels are reached within 2 to 4 h. There is no established correlation between ketotifen blood concentration and its effect on asthma and allergic rhinitis.

### TABLE 3
Effect of nedocromil sodium on exercise-induced asthma in children

<table>
<thead>
<tr>
<th>Authors (reference)</th>
<th>n</th>
<th>Age (years)</th>
<th>Dose</th>
<th>Pulmonary function tests</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauer 1989 (43)</td>
<td>10</td>
<td>12-15</td>
<td>4 mg (30 min pret)</td>
<td>Specific airway conductance</td>
<td>N&gt;P</td>
</tr>
<tr>
<td>Honniskan 1985 (32)</td>
<td>12</td>
<td>7-14</td>
<td>4 mg (30 min pret)</td>
<td>FEV1, PEFR</td>
<td>N&gt;P</td>
</tr>
<tr>
<td>Chudry et al 1987 (44)</td>
<td>12</td>
<td>6-15</td>
<td>4 mg (30-150 min pret)</td>
<td>FEV1</td>
<td>N&gt;P</td>
</tr>
<tr>
<td>Bauer et al 1986 (46)</td>
<td>20</td>
<td>7-16</td>
<td>8 mg (30 min pret)</td>
<td>FEV1, FEPR</td>
<td>N&gt;P</td>
</tr>
<tr>
<td>Curtis 1993 (46)</td>
<td>12</td>
<td>6-13.5</td>
<td>0.4 mg N:10mg (30 min pret)</td>
<td>FEV1</td>
<td>N&gt;CuP</td>
</tr>
</tbody>
</table>

> More effective: C Sodium cromoglicate; FEV1, PEFR. Forced expiratory flow rate to 76% of forced vital capacity; FEV1. Forced expiratory volume in 1 s: N Nedocromil sodium; P Placebo; PEFR Peak expiratory flow rate

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antithrombotic effect. Its bioavailability is only 50% due to a "first pass" effect. Ketotifen is extensively biotransformed and 60 to 70% of a dose of ketotifen is eliminated in the urine within 48 h (55).

**Mechanism of action**

Our knowledge on ketotifen's mechanism of action is limited and presently under investigation. Experimental evidence suggests antianaphylactic properties substantiated by ketotifen's ability to inhibit the release of mediators of anaphylaxis such as the slow reacting substance of anaphylaxis, and the inhibition of calcium uptake in isolated mast cells and in smooth muscle (56-58). In animal models of passive cutaneous anaphylaxis, ketotifen inhibits both passive cutaneous anaphylaxis and histamine-induced reactions (56,57).

Ketotifen also exhibits some antithrombotic properties. In animal studies ketotifen administration before aerosol challenge attenuated bronchoconstrictor eosinophilia (59). Eosinophil recruitment in the tracheobronchial tree and their activation within the lung release cytotoxic proteins and potent inflammatory mediators (delepotriiatrie C4, superoxide [O2·], platelet-activating factor) that will precipitate a cascade of events that will subsequently lead to bronchial hyper-reactivity (55,60). Although ketotifen has no bronchodilator properties, it appears to be capable of increasing both the affinity for the beta-adrenergic receptors and cAMP intracellular concentrations (55).

**Clinical pharmacology**

Acute bronchial challenge: Ketotifen administration has been shown to inhibit the bronchoconstriction caused by either histamine or allerogenic challenge but will not prevent bronchospasm induced by either methacholine inhalation or exercise (55,61-64). Although the number of studies on acute bronchial challenge in children is very limited, they generated results similar to those observed in adults (55,65).

Clinical efficacy: Studies designed to evaluate the efficacy of ketotifen in the treatment of asthma in children have generated conflicting results (66-81). The parameters used to evaluate the efficacy of ketotifen in the treatment of asthma were mainly based on analysis of patients' symptom diaries and bronchodilator requirements. The majority (66%) of the studies (Table 4) reported a decrease in both frequency of symptoms and use of bronchodilators, such as theophylline or beta-agonists, in patients receiving oral ketotifen. These improvements occurred in most instances following long

<table>
<thead>
<tr>
<th>Authors (reference)</th>
<th>N</th>
<th>Age</th>
<th>Dose</th>
<th>Bronchodilator use/ symptoms</th>
<th>Results</th>
</tr>
</thead>
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<tr>
<td>Loper 1985 (67)</td>
<td>60</td>
<td>1-15</td>
<td>0.5-1 mg bid for &lt;12 weeks</td>
<td>Symptoms: L, K = P</td>
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<tr>
<td>Longo et al 1986 (68)</td>
<td>41</td>
<td>4-14</td>
<td>1 mg bid 16 weeks</td>
<td>Symptoms: K, P</td>
<td></td>
</tr>
<tr>
<td>Miraglia et al 1986</td>
<td>33</td>
<td>&lt;3</td>
<td>0.1 mg/kg 12 weeks</td>
<td>Symptoms: L, K = P</td>
<td></td>
</tr>
<tr>
<td>Granieri and Girardi 1988 (70)</td>
<td>50</td>
<td>&lt;10 months</td>
<td>0.35 mg bid 20 weeks</td>
<td>Symptoms: L, K = P</td>
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<tr>
<td>Hoi et al 1988 (71)</td>
<td>30</td>
<td>3-11</td>
<td>0.03 mg/kg bid 12 weeks</td>
<td>Symptoms: L, K = P</td>
<td></td>
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<tr>
<td>Nejami et al 1988 (72)</td>
<td>134</td>
<td>&lt;4</td>
<td>0.5 mg bid 12 weeks</td>
<td>Symptoms: L, K = P</td>
<td></td>
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<tr>
<td>Naspitz et al 1988 (73)</td>
<td>75</td>
<td>8</td>
<td>1 mg bid 20 weeks</td>
<td>Symptoms: L, K = P</td>
<td></td>
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<td>Reid 1989 (74)</td>
<td>189</td>
<td>2-6</td>
<td>1 mg bid 12 weeks</td>
<td>Symptoms: L, K = P</td>
<td></td>
</tr>
<tr>
<td>Rackham et al 1989 (75)</td>
<td>139</td>
<td>5-17</td>
<td>1 mg bid 6 months</td>
<td>Symptoms: L, K = P</td>
<td></td>
</tr>
<tr>
<td>Dawson et al 1989 (76)</td>
<td>65</td>
<td>5-13</td>
<td>1 mg bid 22 weeks</td>
<td>Symptoms: L, K = P</td>
<td></td>
</tr>
<tr>
<td>Gregoros et al 1980 (77)</td>
<td>23</td>
<td>1-5</td>
<td>0.25-0.5 mg bid 8 weeks</td>
<td>Symptoms: L, K = P</td>
<td></td>
</tr>
<tr>
<td>Lotfus and Price 1987 (78)</td>
<td>47</td>
<td>2-6</td>
<td>1 mg bid 24 weeks</td>
<td>Symptoms: L, K = P</td>
<td></td>
</tr>
<tr>
<td>Volovitz et al 1988 (79)</td>
<td>30</td>
<td>1-3</td>
<td>1 mg bid 12 weeks</td>
<td>Symptoms: L, K = P</td>
<td></td>
</tr>
<tr>
<td>White et al 1988 (80)</td>
<td>37</td>
<td>1-6</td>
<td>1 mg bid (&lt;5 years)</td>
<td>Symptoms: L, K = P</td>
<td></td>
</tr>
<tr>
<td>Van Assperen et al 1992 (81)</td>
<td>113</td>
<td>0.5-3</td>
<td>0.5 mg bid 16 days</td>
<td>Symptoms: L, K = P</td>
<td></td>
</tr>
</tbody>
</table>

L: Decrease in symptoms and/or bronchodilator use; No changes; 1: One of five symptoms was ameliorated; 2: Two of four symptoms were ameliorated; = More effective; FEV1: Forced expiratory volume in 1 s; K: Ketotifen; P: Placebo; PEF: Peak expiratory flow
term administration (ie, more than eight weeks). In general, children responding to ketotifen experienced fewer interruptions of therapy and required fewer nocturnal nebulised treatments (71,74). The majority of patients or their parents favoured ketotifen over placebo in their global assessment of the trial.

The information on the effect of long-term ketotifen therapy on spirometric measures of airway obstruction is limited. In one study ketotifen treatment did not improve forced expiratory flow rates at 25% to 75% of forced vital capacity (FVC), but increases in FVEFs and FVC reached statistical significance after six and 10 weeks of ketotifen therapy, respectively (75). In several studies, ketotifen treatment was not associated with improvement of peak expiratory flow rates (74,76,80).

There are few studies comparing ketotifen with sodium cromoglycate and none with nedocromil sodium (82,83). In studies where sodium cromoglycate and ketotifen were administered concomitantly, the addition of ketotifen did not provide any additional benefit to the patient's treatment (55,76). In studies comparing ketotifen with sodium cromoglycate, the two drugs produced similar improvement in asthma symptoms (82,83).

Ketotifen prophylaxis to prevent the development of asthma in selected infants and young children has been evaluated (55,84). Ikua and et al (84) evaluated the prophylactic effect of ketotifen against the onset of asthma in 121 infants with atopic dermatitis without any history suggestive of asthma. Ketotifen (0.1 mg/kg for children weighing less than 14 kg, and 1.2 mg for children weighing 14 kg or more). During the one-year study period, asthma was observed in eight children from the ketotifen group (13.1%) and in 25 children from the placebo group (41.6%) (P<0.001). Although the results of this study are very interesting, further investigations are required before broad use of ketotifen in atopic children can be recommended to prevent the development of asthma.

Ketotifen is generally well tolerated, and the most common side effects are weight gain of 2.8 to 3.3 kg over a one-year period in children less than 12 years of age and drowsiness, which declines over one to two weeks (55).

Pediatric dose

Children between six months and three years of age should be administered 0.5 mg of ketotifen twice daily, while 1 mg should be given to those over three years of age (55).

CONCLUSION

Nonsteroidal anti inflammatory agents clearly have a role to play in pediatric asthma. Sodium cromoglycate and nedocromil sodium are two efficacious antiasthmatic agents that should be used in the treatment of chronic mild to moderate asthma. Several in vitro and adult studies suggest that nedocromil sodium seems to be more potent than sodium cromoglycate; however, similar data are lacking in the pediatric population. Therefore, based on the information available in the pediatric literature, sodium cromoglycate could be the agent of first choice, but nedocromil sodium is certainly a very acceptable alternative.

Sodium cromoglycate and nedocromil sodium can prevent exercise-induced asthma but are less efficacious than beta-adrenoceptor agents. They should be favoured, however, in patients requiring more than one or two treatments per week.

The optimal pediatric dose of nedocromil sodium seems to be 4 mg qd. Although the administration of 20 mg of sodium cromoglycate via a Spinhaler apparatus or by nebulisation qid is adequate, 2 mg of sodium cromoglycate administered with a metered dose inhaler qid may not be optimal for all patients.

Sodium cromoglycate is as efficacious as theophylline and produces significantly fewer side effects, it should be favoured in the treatment of the chronic asthmatic requiring one of these two medications.

The precise role of ketotifen in the treatment of mild chronic asthma remains to be determined. Its role in the 'early prevention' of the development of asthma merits further investigations.

REFERENCES


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