

Pediatric Pharmacotherapy

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Cromolyn and Nedocromil in Children with Asthma

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- [Introduction](#)
- [Mechanism of Action](#)
- [Indications](#)
- [Use in Children](#)
- [Pharmacokinetics](#)
- [Adverse Effects](#)
- [Dosing Recommendations](#)
- [Summary](#)
- [References](#)

Literature Reviews:

- [Antibiotic induced nephropathy](#)
- [Carbamazepine-associated hepatorenal failure](#)
- [Intravenous valproate](#)
- [Ketorolac enantiomer pharmacokinetics](#)
- [Lamotrigine pharmacokinetics](#)
- [Magnesium in Asthma](#)

Formulary Update

Mast cell stabilizers have been used for over a decade in the management of asthma in the United States. These agents are most often used as part of a triple drug regimen which includes corticosteroids and beta-adrenergic agonists to control asthma symptoms, but may be used as single-agent therapy in exercise-induced asthma. This brief review will focus on the use of cromolyn sodium and nedocromil in the pediatric asthmatic population.

Mechanisms of Action

Cromolyn and nedocromil are inhaled anti-inflammatory agents. *In vitro* studies have documented their efficacy in inhibiting the degranulation of mast cells. Stabilizing mast cells prevents the release of inflammatory mediators, including histamine and SRS-A, (slow-reacting substance of anaphylaxis), a leukotriene believed to play an important role in triggering an asthma exacerbation. The exact mechanisms of mast cell stabilization are not fully understood. Recent research with cromolyn has suggested that it indirectly inhibits calcium ions from entering the mast cell and triggering release of cellular contents.^{1,2}

The mast cell stabilizers inhibit both the early and late phases of bronchoconstriction induced by inhaled antigens. In clinical trials, they have been shown to be effective in blunting the response induced by cold air, exercise, sulfur dioxide, environmental air pollutants, and other specific antigenic challenges. Neither agent has bronchodilator, anticholinergic, antihistaminic, or glucocorticoid activity. It is important to note that neither agent is effective in the acute management of a patient experiencing severe bronchoconstriction.^{1,2}

Indications

Both cromolyn and nedocromil are approved by the Food and Drug Administration for the prophylactic management of bronchial asthma. Cromolyn is also approved for the prevention of exercise-induced bronchospasm and, in a nasal spray form, for allergic rhinitis. Cromolyn is approved for children ages 2 years and older, while nedocromil is currently only FDA-approved for children 12 and older.^{1,2}

Use in Children

Despite the lack of full FDA-approval, both cromolyn and nedocromil have been studied in children of all ages.³⁻⁷ Early pediatric studies documented their efficacy as single agents compared to other standard treatments in mild to moderate asthma. More recent studies have focused on their use in patients with more severe disease as an adjunct to other anti-inflammatory and bronchodilator therapies.

Petersen and colleagues gave 62 children (ages 5-15 years) who were already receiving inhaled corticosteroids, a combination of either cromolyn plus terbutaline or terbutaline alone.³ Aerosolized cromolyn was administered in a 10 mg dose three times daily. The corticosteroid dose was then slowly reduced until the patient became symptomatic. Patients receiving cromolyn plus terbutaline were better able to tolerate a reduction in their corticosteroid dose, without worsening asthma symptoms or a need to increase beta-adrenergic use. At the end of the 12 week study period, only one (3.3%) of the cromolyn-treated patients had stopped the steroid taper because of worsening symptoms, compared to 11 patients (34.4%) in the group without cromolyn. The authors concluded that the addition of cromolyn to a regimen including corticosteroids may allow for significant reduction in dosage and potential steroid-associated toxicity. In children with mild to moderate disease, cromolyn may even replace the need for chronic corticosteroids.

The addition of nedocromil to standard asthma regimens has shown similar results. In 1993, Armenio and coworkers documented the benefits of nedocromil in a randomized, double-blind, placebo-controlled trial in 209 children (ages 6-17 years) with asthma.⁴ A nedocromil dose of 4 mg inhaled four times daily was compared to placebo by evaluating asthma symptom diaries, pulmonary function tests, and inhaled beta-adrenergic agonist use. At the end of the 12 week study, total symptom scores had decreased 50% from baseline in the nedocromil group compared to only 9% in the control group. Significant differences were also noted in pulmonary function testing and in the reliance on bronchodilators in the study subjects, when compared to the placebo group.

There are several papers documenting the efficacy of mast cell stabilizers in the prevention of exercise-induced asthma in children. In 1994, de Benedictis and colleagues from the University of Perugia performed a double-blind placebo-controlled crossover trial to compare the efficacy of cromolyn and nedocromil in exercise-induced asthma.⁵ Both drugs and placebo were delivered by metered dose inhaler. Seventeen children (ages 7-15 years) participated. All participants were receiving other medications for their asthma. These other therapies were held for 12 hours prior to testing. Efficacy was assessed by the amount of change in pulmonary function tests. A smaller decrease in FEV₁ (forced expiratory volume in 1 second) after exercise testing represented improved tolerance. The mean and standard deviation for the maximum percentage drop in FEV₁ was 27.4±17.3% for the placebo group versus 14.0±14.6% for cromolyn and 14.4±11.1% for nedocromil.

These results demonstrate the protective effect of mast cell stabilizers on exercise-induced decreases in lung function. The difference between the cromolyn and nedocromil treatment groups were not significant. The same investigators have also found no difference in the duration of action of these two agents or in overall clinical response using similar testing environments.^{6,7}

Pharmacokinetics

After inhalation, less than 10% of a dose of cromolyn or nedocromil is absorbed from the lung. Peak serum concentrations occur within 10-15 minutes of inhalation. Any cromolyn that is systemically absorbed is rapidly excreted in the bile and urine, with a half-life of approximately 1-2 hours. Nedocromil is also rapidly excreted, with an estimated serum half-life of 3 hours in adults. Neither cromolyn nor nedocromil is metabolized.^{1,2,8} Neither drug has been studied in children to determine pharmacokinetic differences compared to adults.

Adverse Effects

The most frequently reported adverse effects with these agents are bronchospasm, cough, or pharyngeal irritation following inhalation. In clinical trials, these reactions occurred in 5-10% of patients. Other adverse effects include laryngeal edema, nasal congestion, wheezing, dizziness, and headache, all occurring in 1-2% of patients. Nausea and vomiting may occur in those patients who swallow a significant part of dose for

inhalation.^{1,2,9,10} In addition to these more common adverse effects, there are three reports of dysuria with cromolyn use, related to excessive systemic drug absorption.⁹

Hypersensitivity reactions to mast cell stabilizers occur in less than 1% of patients treated. IgE-mediated reactions have been documented with both cromolyn and nedocromil, with patients developing a rash, urticaria, or angioedema. Cases involving more severe immune responses, including pulmonary eosinophilic infiltrates and allergic granulomatosis, have also been reported with cromolyn use.^{11,12}

Dosing Recommendations

Cromolyn is available in two forms for the management of asthma: a 10 mg/ml solution for nebulization and an aerosol for inhalation that delivers 800 mcg per spray. Patients receiving cromolyn should begin therapy with 20 mg (nebulized) or 2 sprays (by aerosol) inhaled 4 times daily for prophylaxis. Patients with exercise-induced asthma should inhale 20 mg (nebulized) or 2 sprays (by aerosol) within 1 hr prior to exercise. Children less than 6 years of age may respond to lower doses.¹

Nedocromil is available in an aerosol dosage form which provides 1.75 mg per actuation. The recommended dose is 2 inhalations 4 times daily at regular intervals for prophylaxis. Some patients can achieve satisfactory effects with reduced dosing, using nedocromil only 2 to 3 times daily.²

Patients receiving either of these agents should be instructed that these agents are not effective for acute asthma exacerbations. In order to gain the most benefit from mast cell stabilizers in managing asthma, these agents must be taken on a regular basis, even when the patient is asymptomatic. Parents of young children should be instructed on how to administer the drug to their children and methods for cleaning and storing the aerosol or nebulizer equipment.

Symptomatic improvement typically occurs within 4 weeks of initiating therapy with a mast cell stabilizer. Outcome also may be assessed by the ability to reduce the dose of other asthma therapies associated with more significant dose-related adverse effects, such as steroids, beta-adrenergic agonists, or methylxanthines.

Summary

Mast cell stabilizers are useful adjuncts to therapy with corticosteroids and beta-adrenergic agonists in children with asthma. Both cromolyn and nedocromil have little systemic absorption after inhalation and are well tolerated. These agents may provide better control of asthma symptoms in children and allow a reduction in the doses of therapies with more significant adverse effects.

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Literature Review

Antibiotic-induced nephropathy

This extensive review covers the antibiotics commonly used in the neonatal period and their potential for inducing renal dysfunction. The authors discuss well-known nephrotoxins such as aminoglycosides and vancomycin, as well as less frequently reported causative agents such as the beta-lactams. A thorough description of the mechanisms for drug-induced nephrotoxicity is also included. Fanos V, Cataldi L. Antibacterial-induced nephrotoxicity in the newborn. **Drug Safety** 1999;20:245-67.

Carbamazepine-associated hepatorenal failure

A 6 year-old boy receiving carbamazepine for partial seizure disorder who developed acute hepatic and renal dysfunction is described in this report. The patient had been receiving carbamazepine (40 mg/kg/day) for approximately 3 months prior to this event. He was admitted with symptoms of lethargy and increased seizure frequency. Laboratory values on admission revealed a blood urea nitrogen (BUN) of 67 mg/dl and a serum creatinine of 3 mg/dl. Liver function tests were all significantly elevated. A carbamazepine serum concentration at presentation was 17.7 mcg/ml, despite having missed two doses. Carbamazepine was discontinued and the patient recovered over a period of two weeks. Anticonvulsant therapy was switched to lamotrigine. This case, while not the first to describe these adverse effects, is useful reminder of the ability of carbamazepine to cause both hepatic and renal toxicity. Haase MR. Carbamazepine-induced hepatorenal failure in a child. **Pharmacotherapy 1999;19:667-71.**

Intravenous valproate

Three cases are presented in this article to highlight the utility of the intravenous dosage formulation of valproate in children with status epilepticus. The authors also performed a pharmacokinetic analysis of serum valproate levels in two of the children. Following a loading dose of 20 mg/kg, a maintenance infusion of 4-6 mg/kg/hr provided serum concentrations from 66-92 mg/L, within the therapeutic range. Mean apparent volume of distribution was 0.29 L/kg, with a clearance of 63-66 ml/hr/kg. The authors suggest that initial dosing should reflect prior exposure to anticonvulsants which induce hepatic enzymes: 1 mg/kg/hr in patients without prior drug exposure, 2 mg/kg/hr in patients on prior inducer therapy, and 4 mg/kg/hr in patients currently receiving high-dose pentobarbital. Hovinga CA, Chicella MF, Rose DF, et al. Use of intravenous valproate in three pediatric patients with nonconvulsive or convulsive status epilepticus. **Ann Pharmacother 1999;33:579-84.**

Ketorolac enantiomer pharmacokinetics

Ketorolac is supplied as a 1:1 mixture of enantiomers, although almost all of the pharmacologic activity comes from the S form. In this study, the metabolism of the R and S enantiomers of ketorolac were evaluated in 50 children, ages 3 to 18 years. The S form was present in lower concentrations than the R form at all time points sampled. The elimination half-life of the S form was also shorter than the R form. For comparison, the mean half-life of racemic ketorolac in the children studied was 4.0 hours (similar to the R form), while the mean half-life for the S form was only 2.1 hours. The results of this study are similar to data previously reported in adults. They suggested that the duration of drug effect may be significantly shorter than that expected from studies of racemic ketorolac alone. Kauffman RE, Lieh-Lai, MW, Uy HG, et al. Enantiomer-selective

pharmacokinetics and metabolism of ketorolac in children. **Clin Pharmacol Ther** 1999;65:382-8.

Lamotrigine pharmacokinetics

Twelve children receiving lamotrigine were evaluated to determine population pharmacokinetic parameters. This study is unique in that none of the children were receiving other anticonvulsants known to influence lamotrigine metabolism. Each patient received a single dose of 2 mg/kg lamotrigine by mouth. Mean volume of distribution was 1.50 ± 0.51 L/kg and clearance was 0.64 ± 0.26 ml/min/kg. When normalized for weight, these values were found to be higher than those previously reported for adults. Elimination half-life averaged 32 hours in the children, similar to adult values. The authors conclude that higher doses may be needed in children than in adults to achieve adequate serum concentrations. Chen C, Casale EJ, Duncan B, et al. Pharmacokinetics of lamotrigine in children in the absence of other antiepileptic drugs. **Pharmacotherapy** 1999;19:437-41.

Magnesium in Asthma

The case of a 12 year old child given intravenous magnesium sulfate after failing conventional therapy for the treatment of an asthma exacerbation is presented in this brief report. A concise, but thorough, review of the medical literature related to the use of magnesium in asthma is also provided. This short article would be a useful addition to the files of any pediatric practitioner. Dib JG, Engstrom FM, Sisca TS, et al. Intravenous magnesium sulfate treatment in a child with status asthmaticus. **Am J Health-Syst Pharm** 1999;56:997-1000.

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 6/25/99:

1. Trovafloxacin (oral) and alatrofloxacin (intravenous) were removed from the formulary. Trovafloxacin, a fluoroquinolone antibiotic, has been associated with over 100 cases of hepatic toxicity, according to reports from the Food and Drug Administration. Fourteen cases of acute hepatic failure have been reported, including 6 patient deaths.
2. Modafinil (Provigil[®]; Cephalon) was added to the formulary. This drug is an analeptic used in the treatment of narcolepsy. Modafinil is restricted to out-patient use only.



3. Amprenavir (Agenerase[®]; Glaxo-Wellcome) was also added to the formulary. Amprenavir is a protease inhibitor used in combination with other antiretroviral agents in the treatment of HIV infection. The dose for adults and adolescents (13-16 years of age) is 1,200 mg twice daily. The dose for children 4-12 years of age or patients < 50 kg is 20 mg/kg twice daily or 15 mg/kg three times daily for the capsules. An oral solution is also available for children with a recommended dose of 22.5 mg/kg twice daily or 17 mg/kg three times daily. The difference in dosing recommendations reflects the reduced bioavailability of the oral liquid.

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