

variety of systems, including host defense. None of these studies revealed adverse effects of nedocromil sodium at any of the dose levels used. Some short-term effects were noted in single-dose studies in which doses of 2 gm/kg or more were given intravenously (Table I).

On the basis of evidence gathered in animal studies, nedocromil sodium appears to be extremely well tolerated. No potential has been identified for long-term toxic effects on any organ or body system, nor does there appear to be any potential for genotoxic or carcinogenic activity. Moreover, this compound has not demonstrated any adverse effects on the reproductive system or on the normal development of growing animals (from weaning to maturity).

CONCLUSION

In conclusion, nedocromil sodium has a high safety margin. The animal safety data are believed to be relevant to assess safety in humans and support the long-term use of the compound at doses required for therapeutic efficacy. Nedocromil sodium does not appear to have the potential

for causing significant adverse effects by means of exaggerated (or high-dose) pharmacology. The compound has several beneficial effects on a variety of cells and in other test systems relevant to the pathogenesis of asthma.

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An overview of human safety data with nedocromil sodium

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The pharmacokinetic characteristics of nedocromil sodium suggest that this new antiinflammatory agent will be a very safe treatment for asthma. Nedocromil sodium is absorbed from the lung; very little is absorbed from the gastrointestinal tract. It is not metabolized and thus will not compete for metabolic pathways. Nedocromil sodium is not protein bound at a level at which it will displace other compounds. Rapidly cleared from plasma, nedocromil sodium has a very nar-

row range of general pharmacologic effects. Moreover, it has an extremely low level of toxicity in animal models. As described by Dr. Clark at this workshop, the lack of toxicity in animals at doses many magnitudes of the human dose demonstrates a large margin of safety for this drug.

Clearly, what happens in humans is most important, and our means of determining a clinical profile for any drug come from the results of clinical studies. Nedocromil sodium is generally well tolerated. More than 8400 patients have participated in both double-blind controlled and open-label clinical trials of the drug ranging from 2 to 52 weeks. Of these, 5352 patients received nedocromil sodium, 3538 on a four times daily schedule and 1814 on either a twice-daily schedule or some other dose regimen. Approximately 73% of the patients used the study treatment for at least 8 weeks. Adverse events occurring in

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TABLE 1. Adverse events occurring with a frequency of greater than 3% in double-blind, group-comparative clinical trials of nedocromil sodium given four times daily

Adverse event	% experiencing		% withdrawing	
	Nedocromil sodium (n = 2042)	Placebo (n = 1875)	Nedocromil sodium	Placebo
Unpleasant taste*	12.6	3.6	2.1	0.4
Coughing	7.0	7.2	1.4	1.4
Pharyngitis	5.7	5.0	0.6	0.5
Rhinitis*	4.6	3.0	0.1	0.1
Upper respiratory tract infection*	3.9	2.4	0.1	0.1
Bronchospasm†	5.4	8.2	1.5	2.3
Dyspnea	2.8	3.8	0.9	1.3
Nausea*	4.0	2.1	1.3	0.7
Headache	6.0	4.7	0.5	0.3
Chest pain	4.0	3.9	0.9	0.6
Viral infection	2.4	3.4	0.1	0.1

*Statistically significant ($p \leq 0.05$) higher frequency of event in nedocromil sodium-treated group.

†Statistically significant ($p \leq 0.05$) higher frequency of event in placebo-treated group.

double-blind, group-comparative trials at a frequency of greater than 3% are shown in Table 1. A total of 2042 patients received nedocromil sodium, and 1875 patients received placebo in the four times daily studies included here. Of these, 7% of patients treated with nedocromil sodium withdrew from the trials because of adverse events compared with 6% of the placebo-treated patients. The reasons for withdrawal from the placebo-controlled four times daily trials were similar in the nedocromil sodium-treated and placebo-treated groups.

The most commonly reported adverse effect of nedocromil sodium was an unpleasant taste, which was reported by approximately 13% of patients participating in these clinical trials. A small percentage of individuals can taste the drug, whereas most patients do not. Approximately 2% of the patients participating in placebo-controlled four times daily studies of the drug have withdrawn because of taste, and overall less than 3% of patients participating in worldwide clinical trials (open label and controlled) withdrew because of taste. Other adverse events reported by more than 3% of the patients in these clinical trials occurring with significantly greater frequency in the active treatment group were rhinitis (4.6% nedocromil sodium, 3.0% placebo), nausea (4.0% nedocromil sodium, 2.1% placebo), and upper respiratory tract infection (3.9% nedocromil sodium, 2.4% placebo). Bronchospasm occurred significantly more frequently in the placebo-treated

group (8.2%) compared with nedocromil sodium-treated patients (5.4%). Pre- and posttreatment assessments of laboratory variables have shown elevations of SGPT in 3.3% of patients receiving nedocromil sodium versus 1.7% of patients receiving placebo. The average elevation over placebo was 10 IU and because no patient became ill the clinical significance of these elevations is unclear. By far the most common event causing patients to withdraw from clinical studies was increasing asthma severity, which occurred more frequently in the placebo group than in the nedocromil sodium-treated group.

Clinical experience during open assessments with nedocromil sodium for as long as 12 months has also shown that nedocromil sodium remains well tolerated.^{1, 2} Furthermore, in these studies, the patients' asthma remained stable throughout the study despite reductions in concomitant medications in many cases.

Nedocromil sodium has been available in the United Kingdom since 1986, and a large body of human safety data has been derived from the Prescription Event Monitoring program in that country. This national program provides the means to follow up on adverse events in patients using a particular drug. The program operates as follows: all prescriptions for drugs are sent to a central clearing house where the government pays for them. At this point, prescriptions for certain selected treatments can be identified for specific follow-up by another agency. This agency then

asks the prescribing physician to report back on any unusual symptoms or events that have occurred since the prescription was dispensed. More than 14,000 patient reports on nedocromil sodium have been gathered from the United Kingdom with the use of this method. These reports have generated no new or unexpected findings. The only features reported with any incidence are unpleasant taste, occasional headache, and nausea. Similar findings also come from spontaneous adverse event reports from other countries where the drug is marketed.

In summary, laboratory tests, clinical trials, and postmarket experience show that nedocromil sodium is well tolerated by most patients. Adverse

events are generally mild, and the incidence of severe reaction is extremely uncommon. These data indicate that nedocromil sodium has an excellent safety profile, a feature of major importance in the decision to prescribe this drug.

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Highlights of the nedocromil sodium clinical study presentations

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Nedocromil sodium (Tilade) is a new compound for the treatment of asthma: an antiinflammatory pyranoquinoline. It is chemically distinct from β_2 -agonists, corticosteroids, theophylline, and cromolyn sodium, the other agents commonly used to treat asthma patients.

Nedocromil sodium has been studied in placebo-controlled clinical trials at both four times and twice daily dosages. Some of the studies included in the worldwide clinical program assessing the efficacy and safety of nedocromil sodium are described below.

THE NORTH AMERICAN TILADE STUDY GROUP

The U.S. program to assess the clinical efficacy of nedocromil sodium has focused on patients

Abbreviation used

FEV₁: Forced expiratory volume in
1 second

with asthma of mild-to-moderate severity who regularly use theophylline or oral or inhaled β_2 -agonist drugs to control their asthma symptoms. These are the patients who are seen most frequently by clinicians who treat asthma.

The North American Tilade Study¹ was a multicenter, double-blinded trial in which 127 patients with mild-to-moderate asthma who had been maintained on slow-release theophylline and β_2 -adrenergic bronchodilators were randomly assigned to receive either nedocromil sodium or placebo four times a day for 14 weeks. Patients were started on treatment after a 2-week baseline period. Slow-release theophylline was withdrawn after 2 weeks of treatment and regularly used oral β_2 -adrenergic agents were discontinued at the sixth week of treatment. In this study patients on nedocromil sodium showed statistically significant reductions in their daytime and nighttime symp-

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