Inhibition of different dosages of oxatomide or placebo on skin prick test and nasal allergen provocation

Giorgio L. Piacentini, MD, Diego G. Peroni, MD, Luciano Sette, MD, Cecilia Bonizzato, MD,* Monica Benedetti, MD,* and Attilio L. Boner, MD
Misurina and Verona, Italy

In this two-stage, double-blind study, we evaluated the effects of different dosages of oxatomide (1 and 2 mg/kg/day) on nasal provocation and skin reaction wheal induced by grass-pollen challenge. Children with a positive history of allergic rhinoconjunctivitis and positive responses to skin prick test and nasal provocation test to grass pollen were studied out of season. The results obtained with 1 mg/kg/day of oxatomide demonstrated no significant difference in wheal areas and nasal secretion induced by allergen challenge between treated and untreated patients. The administration of 2 mg/kg/day demonstrated a significant suppression in wheal reaction and nasal secretion induced by specific challenge. (J ALLERGY CLIN IMMUNOL 1991;88:218-25.)

Key words: *Oxatomide, antihistamines, children, rhinitis, prick test, nasal challenge*

Oxatomide, 1(3-(4(diphenylmethyl)-1-piperazinyl) propyl)-1,3dihydro-2H-benzimidazol-2-one, is an orally active H_1-histamine receptor antagonist and inhibitor of mast cell degranulation.[1-3] Since histamine is only one of the mediators contributing to the pathophysiology of the allergic reaction,[4] inhibition of mast cell mediator release may be a very effective tool in the management of allergic diseases.

The present two-stage, double-blind study was designed to evaluate the protective effect of different dosages of oxatomide (Tinset; Puropharma, Milan, Italy) on SPT and allergen-induced nasal symptoms in allergic children.

Abbreviations used
SPT: Skin prick test
NPT: Nasal provocation test
AUR: Antigen unit of RAST
HSA: Human serum albumin

MATERIAL AND METHODS

Patients

Two age-matched groups of children with positive histories of seasonal allergic rhinitis and positive response to SPT and NPT with grass pollen entered the study. Patients' characteristics are summarized in Table I. In the first stage, 20 children, 17 male and three female children, ranging from 9 to 14 years (mean ± SD, 12.1 ± 0.5), received oxatomide (1 mg/kg/day) or placebo. In the second stage, another group of 20 children, 15 male and five female children, ranging from 7 to 14 years (mean ± SD, 10.9 ± 0.6), received oxatomide (2 mg/kg/day) or placebo. The same preparations of oxatomide (oral suspension, 25 mg/ml) and placebo (inactive ingredients plus oxatomide vehicle) were used for the two stages of the study. Drug or placebo were administered during a fasting state in the morning and just before dinner, at least 6 hours after lunch.

Patients stopped all drugs, including antihistamines, cromolyn, topical corticosteroids, and nasal decongestants at least 2 months before the study period. No drug, other than oxatomide, was allowed during the study period. None of the children had a history of an upper respiratory tract infection within 1 month of, or during, the study period.

Informed consent was obtained from the patients' parents. The study protocol was approved by the ethical hospital committee.

SPT

Tests were performed on the volar aspect of the forearm. Each patient was tested with the same batch of freeze-dried grass-pollen extract (Bayropharm Italiana; Milan, Italy) diluted in 50, 200, and 800 AUR/ml in HSA. Histamine (10 mg/ml) and HSA were used as positive and negative controls. Reconstitution and dilution of the allergen were made with serum albumin diluent at the time of each test. The

From the Department of Pediatrics, University of Verona, and *Istituto Pio XII, Misurina (BL), Italy.
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Reprint requests: Attilio L. Boner, MD, Clinica Pediatrica, Universita' di Verona, Policlinico B. Roma, 37134 Verona, Italy.
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TABLE I. Patients' characteristics

	Stage 1		Stage 2	
	Oxatomide	Placebo	Oxatomide	Placebo
Sex (M/F)	7/3	10/0	6/4	9/1
Age (yr) (mean ± SD)	12.1 ± 2.8	12.2 ± 0.5	10.9 ± 0.6	11.0 ± 0.6
	NS		NS	
Weight (kg) (mean ± SD)	39.0 ± 2.8	42.3 ± 3.5	44.7 ± 4.2	40.2 ± 2.7
	NS		NS	
Height (cm) (mean ± SD)	145.4 ± 3.4	149.5 ± 3.8	146.4 ± 3.9	147.4 ± 4.3
	NS		NS	
SPT positivity (No. of subjects)				
Only grass pollen	3/10	0/10	0/10	0/10
Grass pollen plus *Dermatophagoides*	6/10	10/10	10/10	10/10
Grass pollen plus *Parietaria*	1/10	0/10	0/10	0/10
Duration of allergic rhinitis (yr) (mean ± SD)	7.8 ± 0.9	9.0 ± 0.7	5.3 ± 0.5	5.6 ± 0.4
	NS		NS	

NS, No significant difference.

TABLE II. SPT wheal mean areas induced by histamine and grass pollen (AUR 50, 200, and 800) before and after treatment with oxatomide or placebo*

	Oxatomide		Placebo	
	Before	After	Before	After
Stage 1 (oxatomide, 1 mg/kg/day)				
Histamine (10 mg/ml)	35.5 ± 3.9	21.4 ± 5.1	30.5 ± 3.0	30.0 ± 3.5
	NS		NS	
AUR				
50	16.9 ± 13.1	12.2 ± 10.6	13.0 ± 6.8	12.4 ± 6.4
	NS		NS	
200	25.4 ± 17.5	19.5 ± 14.3	19.1 ± 10.5	22.1 ± 16.1
	NS		NS	
800	24.8 ± 5.1	24.1 ± 13.8	27.4 ± 7.7	35.5 ± 11.4
	NS		NS	
Stage 2 (oxatomide, 2 mg/kg/day)				
Histamine (10 mg/ml)	22.3 ± 8.5	10.1 ± 5.2	25.6 ± 9.0	28.7 ± 12.7
	$p < 0.002$		NS	
AUR				
50	12.2 ± 11.4	3.1 ± 5.5	10.0 ± 5.6	8.0 ± 4.8
	$p < 0.05$		NS	
200	19.7 ± 11.6	7.1 ± 7.3	16.1 ± 7.8	14.7 ± 9.2
	$p < 0.05$		NS	
800	34.7 ± 21.8	10.2 ± 7.2	26.6 ± 16.1	21.4 ± 11.2
	$p < 0.05$		NS	

NS, No significant difference.
*Values are expressed as mean ± SD.

outlines of the induced wheal were marked with a pen 15 minutes after pricking and transferred to a paper sheet by a transparent tape. The areas of the wheals were measured by planimetry with 5 mm^2 minimum measurable area and expressed in square millimeters. Flares were not considered in the data collection and evaluation.

NPT

Increasing concentrations (50, 100, 200, 400, and 800 AUR/ml) of freeze-dried grass-pollen extracts reconstituted in HSA were delivered by a metered-dose pump spray in the less congested nostril while patients held their breath. HSA was used to determine the baseline parameters for each

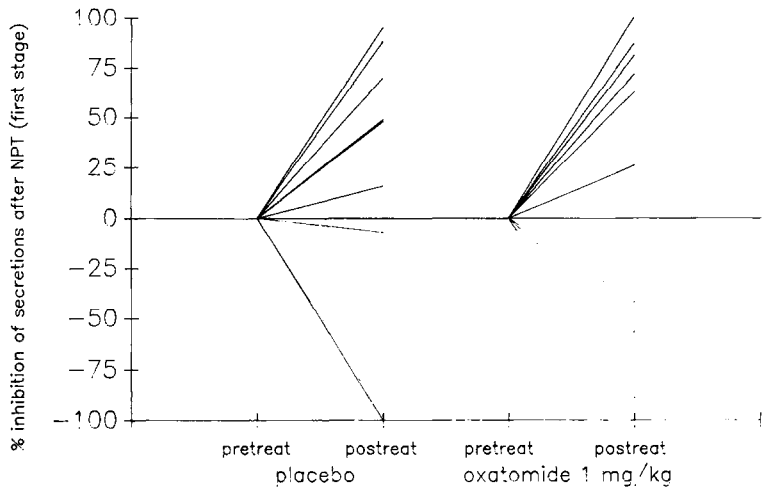

FIG. 1. Percent inhibition of secretions after NPT in the first stage of the study.

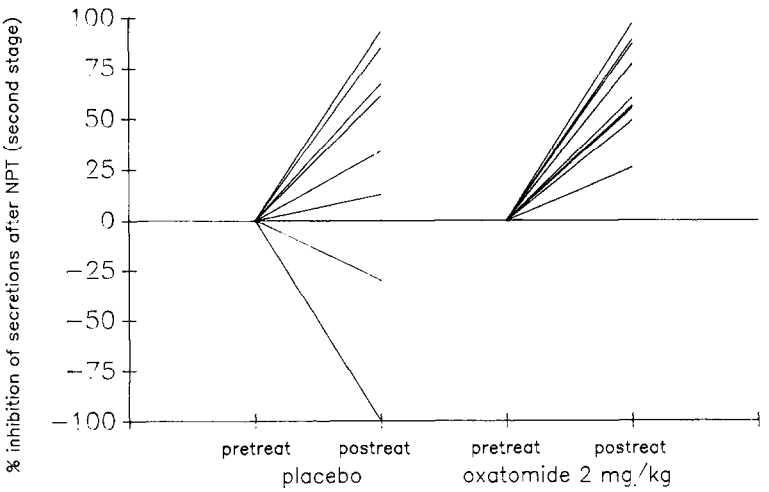

FIG. 2. Percent inhibition of secretions after NPT in the second stage of the study.

patient. Increasing concentrations of allergen were delivered every 30 minutes until a sufficient nasal response, according to the guidelines suggested by Bousquet et al.,[5] was reached. The number of sneezes and amount of secretions, quantitatively expressed as net increase in weight of paper handkerchiefs, available as needed, were considered in the symptom evaluation.

Study design

The study was performed at high altitude (Misurina, 1756 m, Italian Dolomites) during the spring months. At that time, the area was still covered with snow, and no grass pollen was present in the atmosphere. SPT and NPT were performed on each patient at the beginning of the study period and then repeated after 1 month of treatment with oxatomide or placebo. Both tests were performed in the morning, always at the same time for each patient, to minimize the possible influence of circadian variations. The final NPT was performed on each patient with his/her own individual provocative dose.

Side effects for each patient were carefully monitored and recorded throughout the study.

Data were statistically evaluated by Student's t test on a personal computer IBM PS2-55SX (International Business Machines Corp., Armonk, N.Y.).

RESULTS

All the patients completed the study. SPT results for both stages of the study are summarized in Table II. In the first stage (oxatomide, 1 mg/kg/day, or placebo), histamine- and allergen-induced wheals demonstrated no significant reduction ($p > 0.05$) in either oxatomide-treated or placebo-treated patients. In contrast, in the second stage, a significant reduction in both histamine ($p < 0.02$) and allergen-induced

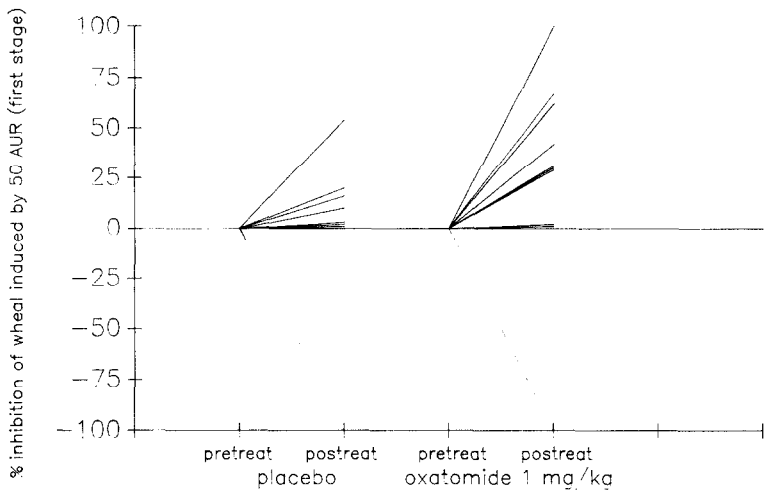

FIG. 3. Percent inhibition of wheals induced by 50 AUR of allergen in the first stage of the study.

TABLE III. Effects of NPT on sneezings (number) and secretion (grams) before and after oxatomide or placebo treatment*

	Oxatomide		Placebo	
	Before	**After**	**Before**	**After**
Stage 1 (oxatomide, 1 mg/kg)				
Sneezings	6.8 ± 4.2	2.8 ± 3.0	5.2 ± 2.8	2.2 ± 1.8
	$p < 0.02$		$p < 0.01$	
Secretion	1.72 ± 1.10	1.44 ± 1.34	1.51 ± 1.51	1.25 ± 1.09
	NS		NS	
Stage 2 (oxatomide, 2 mg/kg)				
Sneezings	5.1 ± 1.8	0.3 ± 0.6	7.2 ± 6.3	3.6 ± 4.0
	$p < 0.01$		$p < 0.02$	
Secretion	2.74 ± 1.06	0.84 ± 0.81	2.22 ± 1.59	1.56 ± 1.38
	$p < 0.01$		NS	

NS, No significant difference.
*Values are expressed as means ± SD.

wheal ($p < 0.01$) for all tested concentrations occurred in the patients treated with oxatomide, 2 mg/kg/day, but not in the placebo-treated control group. The percent inhibition obtained in each patient is illustrated in Figs. 1 and 2. Comparison of potency of oxatomide in the suppression of histamine-induced versus allergen-induced wheals was also evaluated. In the first stage, oxatomide, 1 mg/kg/day, caused a 48% reduction in histamine-induced wheal reactions and 36%, 31%, and 23% reductions for 50, 200, and 800 AUR/ml allergen-induced wheal reactions, respectively. In the second stage, oxatomide, 2 mg/kg/day, caused a 53% reduction in histamine-induced wheal reactions and 78%, 80%, and 64% reduction for 50, 200, and 800 AUR/ml allergen-induced reactions, respectively. The results of the NPT are summarized in Table III. There was no significant difference in baseline reactivity to HSA among the four groups of subjects ($p > 0.05$). During the first stage, a significant reduction in the number of sneezes was observed both in oxatomide-treated ($p < 0.02$) and placebo-treated children ($p < 0.01$). In contrast, no significant difference ($p > 0.05$) in the weight of the secretion between the beginning and the end of the study was demonstrated in either actively treated or the placebo-treated group. A significant reduction in the number of sneezes was also observed in both oxatomide- ($p < 0.01$) and placebo-treated patients ($p < 0.02$) during the second stage of the study. In this stage, the weight of the nasal secretions was significantly reduced in the actively treated group ($p < 0.01$) but not in the control group ($p > 0.05$). The percent inhibition of nasal parameters for each patient is illustrated in Figs. 3 to 8.

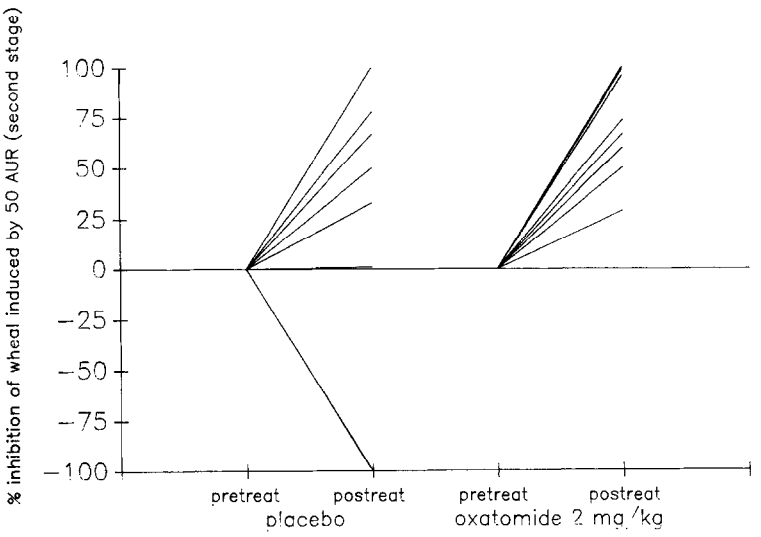

FIG. 4. Percent inhibition of wheals induced by 50 AUR of allergen in the second stage of the study.

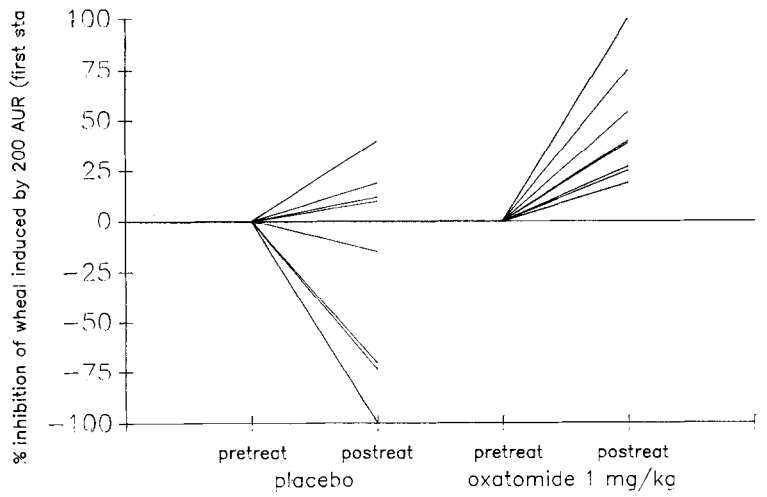

FIG. 5. Percent inhibition of wheals induced by 200 AUR of allergen in the first stage of the study.

During the first stage, one of the oxatomide (1 mg/kg/day)-treated childen demonstrated mild irritability. In the second stage, two of the children treated with oxatomide at the dosage of 2 mg/kg/day demonstrated drowsiness, more evident in the first days of treatment. One child in the placebo-treated group complained of headache.

DISCUSSION

NPT and SPT have been demonstrated to correlate well with the release of mediators in nasal secretions and with symptom-medication scores during the pollen season.[6, 7] Therefore, they are used extensively in studies evaluating the efficacy of antihistamines.[8, 9]

The results of this study suggest that oxatomide, at the dosage recommended by the manufacturer (1 mg/kg/day), does not significantly suppress either the SPT wheal induced by histamine or allergen or the NPT rhinorrhea induced by a specific allergen. In contrast, protective effects in prevention of nasal symptoms (sneezing and rhinorrhea) during specific NPT and in reduction of wheal reactions induced by specific SPT are demonstrated with the administration of oxatomide, 2 mg/kg/day.

From the comparison of potency of oxatomide in the suppression of histamine-induced wheal versus allergen-induced wheal, it may be possible to address specific H_1-receptor antagonist activity versus mem-

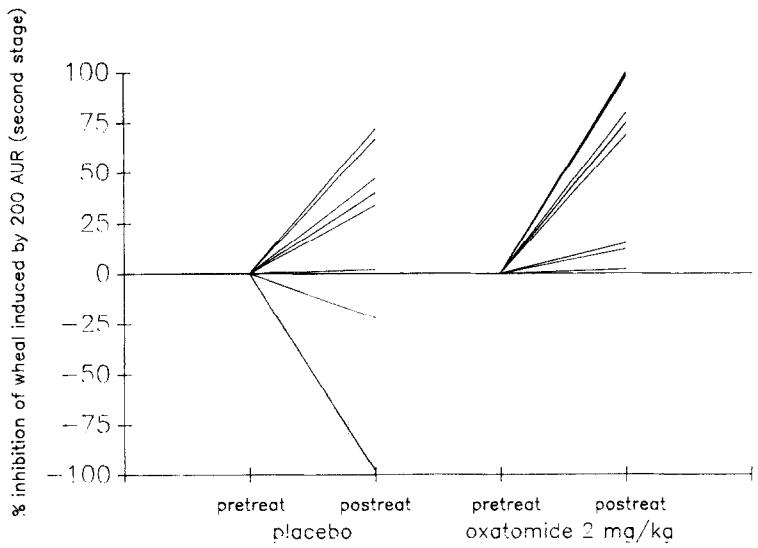

FIG. 6. Percent inhibition of wheals induced by 200 AUR of allergen in the second stage of the study.

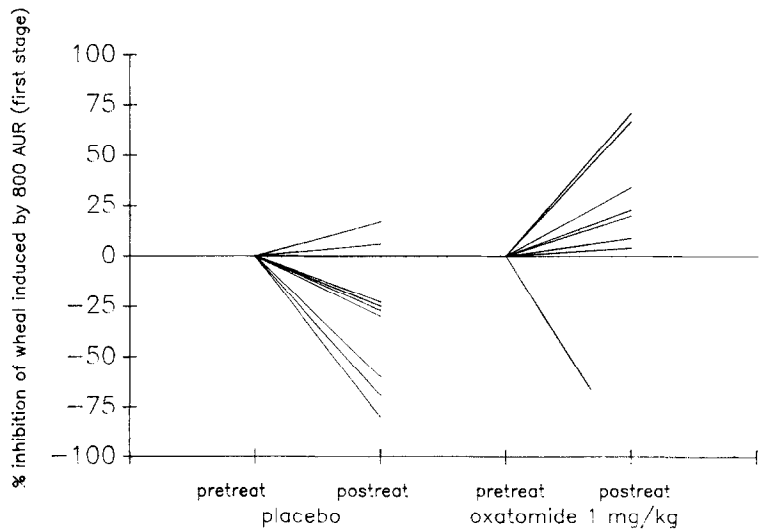

FIG. 7. Percent inhibition of wheals induced by 800 AUR of allergen in the first stage of the study.

brane stablization. At the smaller dosage of 1 mg/kg/day, oxatomide caused greater suppression of histamine-induced wheal (about 48%) than allergen-induced wheal (about 36%, 31%, and 23%, respectively, for 50, 200, and 800 AUR/ml). In contrast, the larger dosage of 2 mg/kg/day resulted in a higher level of suppression of allergen-induced wheal (about 78%, 80%, and 64%, respectively, for 50, 200, and 800 AUR/ml), whereas suppression of histamine-induced wheal remained approximately the same (about 53%). Therefore, at the larger dosage, oxatomide may have an additive effect of prevention of mast cell degranulation and release of mediators or may have specific antagonism of mediators other than histamine.

Previous studies with other H_1-receptor antagonists have also failed to be effective in suppressing the wheal-and-flare response when the drugs were administered according to the dosage suggested by the manufacturer.[8, 10] Simons et al.[10] demonstrated that a 0.04 mg/kg single dose of triptolidine (initial recommended dosage) in adults had a modest suppressive effect on the histamine-induced wheal-and-flare reaction. Furthermore, Long et al.[8] demonstrated a significant skin test suppression occurring 2 hours after administration of single doses of clorpheniramine (16

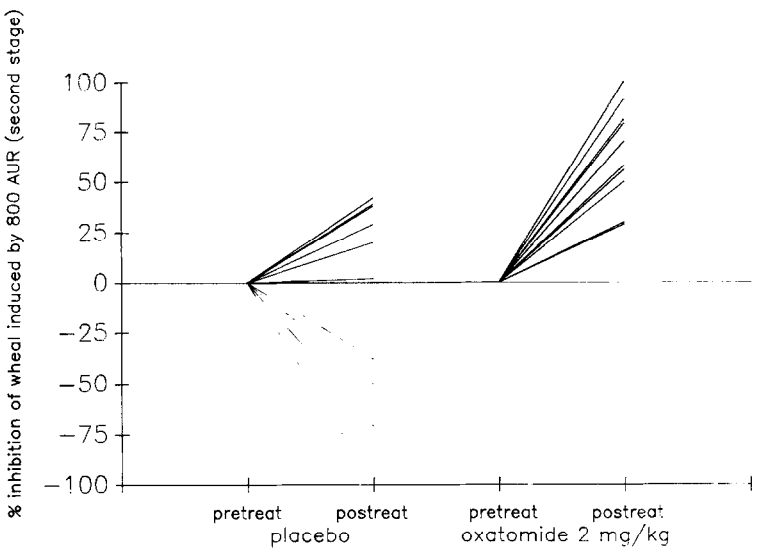

FIG. 8. Percent inhibition of wheals induced by 800 AUR of allergen in the first stage of the study.

mg), hydroxyzine (50 mg), and promethazine (50 mg), but not of tripelennamine (100 mg), diphenhydramine (50 mg), and cyproheptadine (16 mg) in adult patients. These authors concluded that antihistamines, at the recommended dosage, may differ greatly in their suppressive effects on skin test reactivity.

The degree of wheal-and-flare suppression relates to the H_1-receptor antagonist dose as well as to the serum elimination half-life of the drug.[11] Pharmacokinetic studies with oxatomide in adults have elicited peak plasma concentrations occurring within 4 hours of administration of an oral dose of 60 to 120 mg.[12] An elimination half-life of approximately 14 hours was observed after a single 120 mg dose of oxatomide in healthy subjects.[12] With long-term administration, the mean plasma concentrations increased gradually for about 1 week and then remained constant for a period of 6 months.[12] At the present time, no pharmacokinetic studies with oxatomide have been performed in children. Even though a shorter serum elimination half-life for H_1-receptor antagonists have been demonstrated in children,[13-15] increased metabolism in young children cannot explain the failure of our smaller dosage. In fact, it has been demonstrated that the duration of action of H_1 antihistamines is much more prolonged than might be expected in consideration of serum elimination half-life.[10, 11, 16] This point was considered when we designed the present study. Although a crossover design would have been better for the purposes of this study, with such a design, we would have had to consider an extended washout period.

Previous studies with oxatomide in allergic children have demonstrated contrasting results. Two studies found an effect at the dosage of 1 mg/kg/day,[17, 18] but an additional study, performed with a variable dosage from 1 to 2 mg/kg/day, was not able to prove any symptomatic relief in the treatment of seasonal rhinoconjunctivitis.[16]

The positive results and the low incidence of side effects with the administration of 2 mg/kg/day of oxatomide suggest that oxatomide should be used at larger dosages than dosages presently recommended by the manufacturer (1 mg/kg/day). However, a case report of abnormal neurologic reactions in children treated with oxatomide, 2 mg/kg/day,[19] highlights the necessity of additional studies on the safety of such a dose in children.

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