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Cromolyn versus triamcinolone acetonide for youngsters with moderate asthma

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Although both cromolyn (C) and inhaled corticosteroids are anti-inflammatory therapies for childhood asthma, there are few controlled comparisons of these medications for asthma therapy in children. None were conducted in the United States, and none specifically study triamcinolone acetonide (T) versus C. This 12-week evaluation followed 31 youths, aged 8 to 18 years, with moderate asthma who were assigned to receive C or T according to a prerandomized and blinded code. Patients were instructed to take two inhalations from the study metered-dose inhaler (active T or placebo) and to inhale the contents of one study-provided ampule (C, 20 mg, or placebo) from a compressor-driven home nebulizer three times per day. Patients also used albuterol, two inhalations from a metered-dose inhaler, three times a day (before study medication) and, additionally, if needed. Patients maintained a daily diary, recording extra medication use, adverse experiences, peak flow rates morning and night, and asthma symptom scores. Laboratory assessment of pulmonary function was done at 1, 4, 8, and 12 weeks. Cosyntropin challenge and methacholine bronchoprovocation challenge were performed at the beginning and end of the study. C and T provided similar, adequate asthma control. Symptoms of wheezing, cough, and chest tightness decreased, and daily peak expiratory flow rate increased with both regimens compared to during a 2-week baseline when patients received medication only as needed. There was no significant change in methacholine sensitivity and no change in endocrine function, as measured with fasting plasma control before and after administration of cosyntropin. Although there were significant intragroup differences in the T- but not C-treated groups, there were no discernible significant differences between C and T at these dosages. (J ALLERGY CLIN IMMUNOL 1991;88:742-8.)

Key words: Cromolyn, inhaled steroids, triamcinolone, childhood asthma

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Supported by A.S.T.H.M.A., Inc., Seattle, Wash., and Rorer Central Research, Horsham, Pa.

Received for publication Jan. 10, 1991.

Revised May 29, 1991.

Accepted for publication May 31, 1991.

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1/1/31509

Histology of lung biopsy sections from patients with asthma¹ as well as bronchoalveolar lavage cell differentials from these patients attest to the importance of inflammation of the airways in the pathogenesis of asthma.^{2, 3} With this insight, clinicians are now focusing pharmacologic intervention on drugs with apparent anti-inflammatory activity.^{4, 5} Studies on airway hyperresponsiveness indicate that both aerosolized corticosteroids and C are capable of decreasing hyperresponsiveness, presumably because of their anti-

Abbreviations used

T:	Triamcinolone acetonide
C:	Cromolyn
MDI:	Metered-dose inhaler
PFR:	Peak flow rate
PEFR:	Peak expiratory flow rate
PD ₂₀ :	Provocative dose of methacholine causing a 20% fall in FEV ₁
BDP:	Beclomethasone dipropionate
FEF ₂₅₋₇₅ :	Forced expiratory flow rate between 25% and 75%

inflammatory effects.⁶⁻⁹ Although C is accepted as a primary drug for asthma therapy in the United States, it is sometimes regarded as a poor second choice compared to the more potent aerosolized corticosteroids, which are sometimes avoided because of "steroid phobia" on the part of physicians and patients.

This investigation was designed to evaluate the relative safety and effectiveness of C and aerosolized steroid in children and adolescents with moderate asthma, for example, subjects requiring long-term daily therapy for symptom control. The trial design was double-blind, double-dummy, and parallel with patients receiving either C or T. To our knowledge, there are no other published controlled trials of C versus inhaled steroid in children with asthma conducted in the United States. This represents the only study observing specifically T versus C.

MATERIAL AND METHODS

Subjects were youngsters, aged 8 to 18 years. Subjects demonstrated an FEV₁ $\leq 80\%$ of predicted and demonstrated reversibility of $\geq 15\%$ after two inhalations of isoproterenol. Subjects required daily medication with at least two drugs: β -agonist and theophylline or C for asthma management. If subjects fulfilled these criteria and signed an informed consent (and if pertinent, having parents sign), approved by the Western Investigational Review Board (Olympia, Wash.), patients received a baseline evaluation consisting of history and physical examination, complete blood cell count, chemistry screen, urinalysis, and electrocardiogram. Patients were instructed on completing a daily diary, which assessed asthma medication use and the symptoms of wheezing, chest tightness, and cough, according to a numerical scale with 0 for no symptoms and 4 for severe symptoms. They were instructed on keeping a peak flow chart, recording the best of three maneuvers done before taking any medication on awakening and before bedtime. They then received a 2-week washout regimen, during which only β -agonist inhalation as needed and short-acting theophylline as needed were administered. Both C and long-acting theophylline were stopped at this time.

After the 2-week washout period, patients returned to the laboratory between 7 and 9 AM to perform pulmonary func-

TABLE I. Patients' characteristics

	C-treated group	T-treated group
No.		
M	11	11
F	4	5
Age mean (range)		
M	11.0	11.27
F	13.75	10.80
Prestudy medication		
β -Agonist	15	16
C	12	13
T	2	1
C plus T	1	2

tion tests, cosyntropin challenge (morning plasma cortisol level determinations before and 45 minutes after cosyntropin injection), and methacholine bronchoprovocative challenge according to a standardized protocol.¹⁰ PD₂₀ of ≤ 10 mg/ml was required for continuation in the study.

Patients were then assigned to one of two regimens according to a prerandomized code. Patients were instructed to take two inhalations of albuterol from an MDI, to take two inhalations from the study MDI (active T or placebo), and to inhale the contents of one study-provided ampule (C, 20 mg, or placebo) from a compressor-driven home nebulizer three times per day. Since C placebo MDIs were not available, the compressor delivery of C or saline placebo allowed for the preservation of a double-dummy design. Patients were reminded to maintain the daily diary, recording extra medication use, any adverse experiences, PFRs morning and night, and asthma symptom scores.

Patients returned for an interim history and physical examination, pulmonary function tests, and daily diary collection after 1, 4, and 8 weeks. All asthma medications were withheld on these days until after the visits were completed. After 12 weeks, the patients returned for the final interim history and physical and pulmonary function tests. Clinical laboratory tests were repeated, as were cosyntropin challenge and methacholine challenge. Symptom diaries were collected.

Symptom diary comparisons were made within groups with Student's paired *t* tests and between the two groups with an analysis of covariance with the baseline value for an individual as a covariate. Comparison of extra medication use was made with Student's *t* tests, and median amounts were compared with the Mann-Whitney U nonparametric test. Pulmonary function at each visit was compared with Student's *t* tests. Comparison of rates of change of home PEFR over time was analyzed with simple linear regression. The slope of the regression line was used as an indication of the average rate of change during the study period. For the two treatment groups, the average slopes among patients in a group were obtained, and comparisons between mean values were made by use of both the Student's two-sample *t* test and the Mann-Whitney U nonparametric test.

TABLE IIA. Baseline pulmonary function for T- and C-treated groups

Pt No.	T					
	FEV ₁ (L)	% Pred	FEF ₂₅₋₇₅ (L/sec)	% Pred	PEFR (L/min)	% Pred
1	2.41	86	3.16	101	345	89
2	1.66	103	1.63	78	220	92
3	2.36	96	2.65	93	305	89
4	1.88	70	1.41	50	300	81
5	1.17	82	0.86	46	215	101
6	1.93	87	1.58	60	285	90
7	4.08	103	4.60	110	480	114
8	2.60	86	2.23	65	350	109
9	2.23	63	1.35	34	330	74
10	0.50	19	0.29	11	80	22
11	1.73	78	1.74	66	300	94
12	1.71	61	1.23	42	260	67
13	1.58	110	1.53	85	220	103
14	1.75	97	2.25	99	235	89
15	2.50	103	2.67	101	400	116
16	3.71	89	3.05	67	490	98

Pt, Patient; % pred, percent predicted.

RESULTS

Thirty-five patients entered the study, and 31 patients completed the trial. Two patients receiving active C and two patients receiving active T withdrew from the study because of compliance issues. Age and sex distributions of the groups were similar (Table I). Of 16 patients in the T-treated group, 15 had taken C and albuterol as regular medication before the study, two had taken theophylline also as a maintenance medication, and one patient had taken theophylline and albuterol. Of the 15 patients in the C-treated group, 13 had taken C and albuterol regularly before the study, one had taken theophylline also, and two patients had taken theophylline and albuterol.

Among the T-treated group, 13 patients were atopic, based on strong allergy skin test reactivity (prick or 4+ intradermal, positive), whereas 11 C-treated patients were atopic on this basis. Only one patient in each group was purely pollen sensitive; the other patients demonstrated dust mite and/or mold sensitivity also. These two subjects were not studied during their pollen season.

Baseline-visit pulmonary function was similar for the two groups, as presented by raw data (Table IIA) and means (Table IIB). Mean home PFR determinations during the washout period were also similar for the two groups. Mean methacholine sensitivity could be expressed as a PD₂₀ of 0.18 ± 0.16 mg/ml, with a median of 0.10 mg/ml for the C-treated group and 0.23 ± 0.28 mg/ml, median 0.12 mg/ml, for the T-treated group, which were statistically similar.

Baseline and postcosyntropin plasma cortisol determinations were normal for all patients in both groups (Table IIB). Mean baseline levels were 12.4 ± 6.5 µg/ml and 12.5 ± 4.8 µg/ml for the C-treated and T-treated groups, respectively, with responses of 28.8 ± 6.7 µg/ml and 27.6 ± 4.5 µg/ml, respectively.

Symptom changes because of treatment were assessed by comparing diary scores from weeks 9 through 12 of the double-blind trial with scores of the 2-week baseline period. Within the C-treated groups, there was statistically significant improvement in scores of severity of wheezing ($p = 0.033$), chest tightness ($p = 0.048$), and cough ($p = 0.004$). Also, within the T-treated group, there was significant improvement in scores of wheezing ($p = 0.014$), chest tightness ($p = 0.046$), and cough ($p = 0.028$). There were no significant differences, however, between groups for these symptoms (Table III).

Mean values of weekly home PFRs appear in Table IVA. Rates of change in home PEFR over time were analyzed with simple linear regression. The slope of the regression line was used as an indication of the average rate of change during the study period (Table IVB), expressed as the rate of change per week. Each patient was characterized by a slope. A positive slope indicated an increase in PEFR over time, and negative slopes indicated decreases in PEFR over time. For the two treatment groups, the average slopes were obtained and comparisons between mean values were

C

Pt No.	FEV ₁ (L)	% Pred	FEF ₂₅₋₇₅ (L/sec)	% Pred	PEFR (L/min)	% Pred
1	1.45	76	1.07	45	190	68
2	2.23	89	2.00	70	265	77
3	1.68	76	0.97	37	260	82
4	2.37	88	1.62	54	305	82
5	2.12	75	1.71	46	330	86
6	2.29	72	1.08	31	370	91
7	1.87	94	2.04	83	295	101
8	3.08	104	3.00	82	380	93
9	2.22	91	2.25	79	335	97
10	1.34	83	1.48	71	170	71
11	0.98	54	0.97	43	85	32
12	3.27	82	2.42	54	460	79
13	2.13	100	1.86	73	270	88
14	2.17	77	1.87	89	280	79
15	2.37	109	2.39	77	350	159

made with the Student's two-sample *t* test. For the C-treated group, the average change per week of the morning PEFR was 4.55 ± 8.79 (range, 8.44 to 27.55), and for the T-treated group, 4.69 ± 8.24 (range, 2.55 to 23.79), $p = 0.64$. For the C-treated group, the average change per week of the evening PEFR was 3.97 ± 9.48 (range, 11.74 to 29.67), and for the T-treated group, 4.09 ± 6.88 (range, 2.21 to 21.15), $p = 0.87$. Within the C-treated group, the average change (slope) did not differ significantly from zero (corresponding to no change) for morning ($p = 0.065$) and evening ($p = 0.13$) determinations. Within the T-treated group, the average change demonstrated significant improvement for morning ($p = 0.04$) and evening ($p = 0.03$) measurements.

A comparison of office-visit pulmonary function FEV₁, FEF₂₅₋₇₅, and PEFR also revealed similar values and no statistical differences between the groups (Table V). The change in FEV₁ from baseline over time within the C-treated group did not reach significance ($p = 0.13$), whereas for the T-treated group, it did reach significance ($p = 0.016$).

Methacholine sensitivity of most patients was in the moderate to severe range at initiation of the study. Mean PD₂₀ was 0.18 ± 0.16 $\mu\text{g/ml}$ and 0.23 ± 0.28 $\mu\text{g/ml}$ for the C- and T-treated groups, respectively. At the conclusion of the study, mean PD₂₀ was 0.22 ± 0.26 and 0.17 ± 0.20 $\mu\text{g/ml}$ for the C- and T-treated groups, respectively. Neither within-group or between-group changes were significant. Five patients in each group demonstrated decreasing methacholine sensitivity, eight C-treated and

TABLE IIB. Pulmonary function and methacholine sensitivity at baseline

Mean $\pm$ SD	C-treated group	T-treated group
FEV ₁ (L)	2.18 ± 0.61	2.11 ± 0.84
FEF ₂₅₋₇₅ (L/sec)	1.90 ± 0.76	1.96 ± 1.02
PEFR (L/min)	298 ± 90	300 ± 99
Home PEFR		
Mean AM (L/min)	317 ± 77	325 ± 89
Mean PM (L/min)	336 ± 75	342 ± 91
PD ₂₀ (mg/ml)	0.18 ± 0.16	0.23 ± 0.28
Median	0.096	0.12

10 T-treated patients demonstrated increasing sensitivity, and one patient in each group demonstrated no change.

Fasting morning cortisol and cosyntropin response demonstrated no changes during the trial. Means and ranges for cortisol before and after challenge at baseline and conclusion of the study reveal that there was no trend toward a decrease in either baseline or post-challenge cortisol at the study conclusion for either treated group. Initially, one patient in each treated group had a baseline cortisol marginally outside the normal range, whereas all baselines were normal at the conclusion.

Extra use of albuterol actuation and theophylline tablets was tabulated on a weekly basis for each patient. During the 2-week baseline period, the mean number of times per week that two extra actuations

TABLE III. Symptom-score comparisons between baseline and weeks 9 to 12

SYMPTOMS* (group means $\pm$ SD)	C-treated group	T-treated group	Between-group <i>p</i> value
Wheezing			
Baseline	0.97 $\pm$ 0.75	0.95 $\pm$ 0.64	0.88
Weeks 9-12	0.65 $\pm$ 0.64	0.62 $\pm$ 0.48	
Within group <i>p</i> value	0.033	0.014	
Chest tightness			
Baseline	0.90 $\pm$ 0.81	0.88 $\pm$ 0.65	0.62
Weeks 9-12	0.50 $\pm$ 0.53	0.58 $\pm$ 0.49	
Within group <i>p</i> value	0.048	0.046	
Cough			
Baseline	0.72 $\pm$ 0.54	1.00 $\pm$ 0.77	0.45
Weeks 9-12	0.37 $\pm$ 0.36	0.55 $\pm$ 0.44	
Within group <i>p</i> value	0.004	0.028	

*Symptoms rated on a 0 to 4 scale with 0, none; 1, mild, clearly present but causing little discomfort; 2, annoying, but not causing marked discomfort; 3, moderate, causing marked discomfort; and 4, severe, causing interference with sleep or activities.

of albuterol were used by C-treated group patients was 23.00 ± 17.37 , and from the T-treated group, 34.44 ± 21.43 . The mean number of times per week that theophylline (250 mg) tablets were taken by C-treated group patients was 6.76 ± 10.81 , and for the T-treated group, 8.83 ± 15.67 . The mean number of times per week that two extra actuations of albuterol were used by C-treated group patients during weeks 9 through 12 of the study was 2.50 ± 6.15 , and for the T-treated group, 2.86 ± 8.51 ($p = 0.89$, Student's *t* test). The mean number of times per week that theophylline (250 mg) tablets were taken by C-treated group patients during weeks 9 through 12 was 2.25 ± 3.65 , and for the T-treated group, 1.80 ± 5.21 ($p = 0.78$, Student's *t* test). Three patients required prednisone bursts during the study because of respiratory infections. One patient received C and two were receiving T.

At the study conclusion, patients and their families were asked to rate their asthma control during the double-blind trial. Six patients in each group considered themselves improved, six C-treated and seven T-treated patients were unchanged, and one C-treated and three T-treated patients rated themselves as worse. The differences between the C- and T-treated groups were not significant ($p = 0.68$; χ^2).

There were no adverse effects related to medication use. Also, there were no significant changes in laboratory parameters.

DISCUSSION

C and T provided similar, adequate asthma control for these young subjects with moderate asthma. Symptoms of wheezing, cough, and chest tightness decreased similarly for both regimens compared to symptoms during the 2-week baseline when patients

received medication as needed only. This improvement was also reflected in improved daily PEFR. Unexpectedly, there were no changes in airway hyper-responsiveness, as measured with methacholine challenge. There were no changes in endocrine function, as measured with fasting morning plasma cortisol concentrations before and after cosyntropin.

There were significant intragroup differences with T, but not C: change in morning and evening home PFRs and laboratory FEV₁. Perhaps an intergroup difference would have been demonstrable had the study been longer or if the dosage of T had been larger. The dosage that we selected, two actuations twice daily, is in keeping with Food and Drug Administration guidelines for this product. We avoided large dosage and more frequent administration because we wished to evaluate the study preparations as primary therapy for mild to moderate rather than severe asthma.

In retrospect, we question if a longer washout period before initiating the double-blind trial might have allowed us to observe more change in airway hyper-responsiveness. Most of our patients had been successful C users before the trial, an unavoidable situation because of prescribing patterns for patients with mild to moderate asthma in our community. We limited the washout period to 2 weeks because of the history of rather severe symptoms in these patients and our discomfort in prolonging the "as needed" treatment phase. However, we might have erased our ability to detect changes in methacholine sensitivity by beginning the double-blind phase when patients were still manifesting a C effect. Nevertheless, the failure to observe a change in the T-treated group indicates no therapeutic advantage to aerosolized steroid at these doses to improve on the effects of C. In

TABLE IVA. Mean weekly PEFR (liters per minute)

	Baseline	Week 1	Week 4	Week 8	Week 12
T					
AM	5.47 ± 1.57	348 ± 99	346 ± 104	356 ± 101	355 ± 111
PM	5.72 ± 1.62	356 ± 92	367 ± 113	371 ± 98	369 ± 104
C					
AM	5.15 ± 1.32	318 ± 82	323 ± 085	332 ± 83	325 ± 89
PM	5.53 ± 1.31	347 ± 78	339 ± 089	349 ± 84	337 ± 87

TABLE IVB. Comparisons of rates of change of home PEFR

Average slope ± SD	C-treated group	T-treated group	Between-group <i>p</i> value
AM PEFR	4.55 ± 8.79	4.69 ± 8.24	0.64
Within-group <i>p</i> value	0.065	0.04	
PM PEFR	3.97 ± 9.48	4.09 ± 6.88	0.87
Within-group <i>p</i> value	0.13	0.03	

TABLE V. Mean pulmonary function at office visits

	Baseline	Week 1	Week 4	Week 8	Week 12
FEV ₁ (L)					
T	2.11 ± 0.84	2.21 ± 0.82	2.23 ± 0.84	2.30 ± 0.78	2.26 ± 0.89
C	2.18 ± 0.61	2.11 ± 0.56	2.09 ± 0.60	2.18 ± 0.65	2.13 ± 0.60
FEF ₂₅₋₇₅ (L/sec)					
T	1.96 ± 1.02	2.08 ± 0.99	2.15 ± 0.93	2.05 ± 0.94	2.03 ± 1.19
C	1.90 ± 0.76	1.86 ± 0.69	1.78 ± 0.62	1.99 ± 0.70	1.84 ± 0.67
PEFR (L/min)					
T	300 ± 99	326 ± 97	337 ± 114	319 ± 94	310 ± 107
C	298 ± 90	308 ± 80	299 ± 97	313 ± 97	302 ± 98

contrast, there are the somewhat more impressive within-group trends in pulmonary function in the T-treated group, but this observation needs to be tempered by the failure to demonstrate a significant between-group difference. Recent data support the possibility that routine β -agonist use may aggravate bronchial hyperresponsiveness.¹¹ Although this could be the basis for our failure to observe improvement in this variable with either regimen, it would contradict our previous observations of an improvement in hyperresponsiveness with regular use of anti-inflammatory therapy with β -agonist, although not with regular β -agonist alone.¹² Although in retrospect it might have been preferable to use β -agonist on an as needed only basis during the trial, at the time of study conception, we were not aware of the possible adverse effects of β -agonists on bronchial hyperresponsiveness but were concerned that these patients had needed regular bronchodilator therapy in the past.

There are very few references comparing aerosolized steroid with C treatment for asthma. Several studies¹³⁻¹⁶ have demonstrated superiority of inhaled betamethasone valerate to C in children. Since this product is not used in the United States, it is difficult to assess these results in the context of those drugs that U.S. physicians use regularly for asthma care. Svendsen et al.¹⁷ evaluated 38 atopic adult subjects with asthma with a crossover protocol to compare C, 2 mg four times a day, with BDP, 200 μ g twice daily, each used for 8 weeks. Approximately one third of the patients favored C. However, significant advantage for BDP was noted in terms of pulmonary function and decreased bronchial hyperresponsiveness for the group as a whole. They suggest that it is worthwhile to identify the subgroup of patients who do very well taking C to avoid steroid treatment for this population. Perhaps our acceptance of patients who were often moderately stable taking C biased our sample in that we inadvertently identified a similar subgroup.

Francis and McEnery¹⁸ compared C and BDP in 24 children with a crossover trial with 4 weeks receiving each regimen. Although they found BDP to be "slightly superior" to C, the short duration of the treatment regimen may well have biased the study against an optimal C effect. Mitchell et al.¹⁹ found no difference between BDP and C in a double-blind trial of 12 children in which 12-week regimens were used.

In contrast to the results of numerous studies attesting to the anti-inflammatory activity of inhaled steroids and their remarkable clinical benefits is an assortment of studies noting varying degrees of adverse effects related to systemic absorption and topical activity of these preparations.²⁰ Yet, the small doses used in this study are rarely associated with negative outcome. C presents an outstanding safety record but is a much more costly intervention than the steroid alternative. All these factors must be weighed in making therapeutic decisions.

These results support the safety and efficacy of both C and T therapy for management of children and teenagers with moderate asthma. At these approved dosages by Food and Drug Administration, which are commonly used in the United States, there is no obvious therapeutic advantage of one over the other, although a study with a larger number of patients would be needed to conclude with certainty that there are no differences in therapeutic results.

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