

Topical levocabastine is more effective than sodium cromoglycate for the prophylaxis and treatment of seasonal allergic conjunctivitis

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The efficacy, tolerability, and adverse-effect profile of the recently developed, topical antihistamine levocabastine were compared with those of sodium cromoglycate in a 4-week double-blind, placebo-controlled trial in 95 patients with seasonal allergic conjunctivitis. At the end of the trial, global therapeutic efficacy was considered to be excellent or good in 87% of levocabastine-treated patients, as compared with 68% of sodium cromoglycate-treated patients ($P=0.006$) and 63% of those who received placebo ($P=0.05$). After 4 weeks of treatment, levocabastine patients had experienced significantly greater relief from their most severe ocular symptom than patients in the sodium cromoglycate group ($P<0.05$). Furthermore, 37% of levocabastine-treated patients were virtually symptom-free for at least 75% of the treatment period, as compared with only 6% of patients in the sodium cromoglycate group ($P<0.01$) and 4% of those who received placebo ($P<0.01$). Moreover, this trend was maintained on days when the pollen count was high, when the corresponding figures were 33%, 6% ($P=0.02$), and 4% ($P=0.02$), respectively. Levocabastine was well tolerated. Indeed, the incidence of adverse reactions was no greater in the levocabastine group than in the placebo group. Topical levocabastine is an effective and well-tolerated drug for the prophylaxis and treatment of seasonal allergic conjunctivitis.

B. H. Davies, J. Mullins

Asthma and Allergy Unit, Sully Hospital,
Penarth, South Glamorgan CF6 2YA, UK

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Dr B. H. Davies
Asthma and Allergy Unit
Sully Hospital
Penarth
South Glamorgan CF6 2YA
UK

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Seasonal allergic conjunctivitis is thought to affect around 10% of the UK population. A number of therapeutic options are available for the treatment of this condition. Topical corticosteroids may be an effective short-term therapeutic approach; however, they are unsuitable for the long-term treatment of ocular allergy because of the potential risk of adverse effects such as glaucoma and cataracts (1, 5). Sodium cromoglycate is a common topical agent but should be administered for several days before allergen exposure for maximum therapeutic efficacy.

The role of histamine in mediating the symptoms of allergic conjunctivitis has been extensively investigated. Indeed, ocular challenge studies have clearly shown that histamine H_1 -receptors are the main elicitors of ocular allergy (7). Consequently, it is not surprising that H_1 -receptor antagonists are widely used for the treatment of allergic conjunctivitis. Oral antihistamines provide effective symptomatic relief, but have been associated with systemic adverse re-

actions. Topical antihistamines may be preferable, as they will probably provide even more rapid relief from symptoms without producing any undesired systemic effects. Although topical antihistamines have been used therapeutically for some time, they have always been coadministered with a vasoconstrictor, and, as such, have not been suitable for prolonged treatment.

Levocabastine is the first H_1 -antagonist developed for topical application (12). It is a highly potent compound, being at least 15000 times more powerful than chlorpheniramine (6). Importantly, levocabastine has a very fast onset of action. Ocular challenge studies have shown that it is effective within 10 min of instillation (11). Furthermore, conjunctival provocation tests have demonstrated that topical levocabastine is more effective than sodium cromoglycate and placebo eye-drops in preventing ocular allergic reactions (10). The aim of this study was to compare the efficacy, tolerability, and safety of top-

ical levocabastine with those of sodium cromoglycate for the prophylaxis and treatment of seasonal allergic conjunctivitis.

Material and methods

Patients

Patients over 5 years of age with a documented history of allergic conjunctivitis during a previous hay fever season who presented with at least one typical symptom of allergic conjunctivitis (ocular irritation, burning sensation, itch, redness, photophobia, lacrimation, lid oedema, conjunctival oedema) for which treatment was considered to be necessary were eligible for inclusion in this trial. Exclusion criteria included: concurrent infective conjunctivitis, glaucoma or keratitis; use of contact lenses; and severe renal or hepatic dysfunction. In addition, patients undergoing treatment with oral corticosteroids and antihistamines, or sodium cromoglycate and other topical ocular medications were excluded from this study unless such treatment was discontinued in time for sufficient washout to occur (1 week for corticosteroids, 1 month for astemizole, 3 d for all other drugs).

The study protocol was approved by the local ethics committee, and all patients gave their written, informed consent.

Methods

A total of 95 patients participated in this double-blind, parallel-group trial. Patients were randomized to receive either topical levocabastine (0.5 mg/ml), topical sodium cromoglycate (20 mg/ml), or matching placebo eye-drops, one drop in each eye four times daily for a period of 28 d. Twenty-eight patients were randomized to receive levocabastine, 32 were assigned to receive sodium cromoglycate, and the remaining 29 patients received placebo.

Oral terfenadine was permitted as a rescue medication if ocular symptoms became intolerable. Beclomethasone or budesonide nasal spray was permitted for the relief of severe nasal symptoms.

Grass pollen counts were performed daily during the study period. Days when the pollen count was greater than or equal to $50/\text{m}^3$ were classed as high-pollen days, and days when the pollen count was less than $50/\text{m}^3$ were classed as low-pollen days, unless the preceding day had been a high-pollen day, in which case such days were also considered to be high-pollen days.

Efficacy assessments

Symptoms of ocular irritation, burning sensation, itch, redness, photophobia, lacrimation, lid oedema,

and conjunctival oedema, as well as nasal symptoms, were assessed by the investigator at the time of entry into the trial, after 2 weeks of treatment, and at the end of the study. Symptom severity was graded on a scale from 0 to 3 (0 = absent; 1 = mild; 2 = moderate; 3 = severe). The same symptoms were assessed by the patients on a daily basis by a visual analogue scale (VAS; 0 = no symptoms, 100 = extremely severe symptoms) and recorded on a diary card. Patients were also asked to record consumption of study medication, use of rescue medication, and any adverse reactions on these diary cards. At the end of the trial, both the patients and the investigator provided a global evaluation of treatment efficacy, rating it as excellent, good, moderate, or poor.

Clinical chemistry tests were performed at the beginning and end of the trial. In addition, plasma concentrations of levocabastine were determined at the end of the study period. Body weight was also recorded at the start, after 2 weeks of treatment, and at the end of the trial.

Statistical analysis

The area under the curve (AUC) for the VAS scores (expressed as a percentage of the maximal AUC and calculated by the trapezoidal rule) was derived from the patient diary cards. In addition, the mean severity score for the individual symptoms and the mean severity score for the most severe ocular symptom after 2 weeks of treatment and at the end of the study period were calculated. The percentage of patients in each group who were virtually symptom-free ($\text{VAS} \leq 10$) for at least 75% of the time and the percentage of patients with mild or moderate symptoms ($\text{VAS} \leq 50$) for at least 75% of the time were calculated for the entire study period, as well as for days when the pollen count was high and days when the pollen count was low. These efficacy criteria of 75% were selected because of the relatively high placebo effect associated with the use of eye-drops for the treatment of ocular allergy which may mask the true clinical efficacy of the study drug. A placebo response as high as 40% has been reported for eye-drops (6).

Intergroup variance between all three treatment groups was assessed for significance by the Kruskal-Wallis one-way analysis of variance. All intergroup comparisons between two groups were made by Fisher's exact probability test and the Mann-Whitney U-test.

Results

Of the 95 patients recruited, six were excluded from the efficacy analysis because they dropped out after less than 11 d of treatment. Two patients from the

levocabastine group were lost to follow-up, three patients (one from the levocabastine group and two from the placebo group) withdrew because of adverse effects, and one patient from the placebo group discontinued because of treatment inefficacy. Patient demographics are shown in Table 1. There were no significant intergroup differences at base line. Compliance with study medication was similar in all three treatment groups.

Of the 89 patients retained for the efficacy analysis, a total of 12 patients (five levocabastine patients, two sodium cromoglycate patients, and five placebo patients) failed to complete the full 28-d treatment period and provided data only during the first 2 weeks of the trial. Two of these 12 patients withdrew prematurely because of adverse effects (one patient from the levocabastine group and one from the placebo group), three patients discontinued because of treatment inefficacy (one levocabastine and two placebo patients), and another four discontinued because they were free from symptoms (one levocabastine, one sodium cromoglycate, and two placebo patients). In addition, three patients were lost to follow-up (two from the levocabastine group and one from the sodium cromoglycate group).

Pollen counts were low for the first 10 d of the study, but were generally high for the rest of the study period. Pollen counts were classed as high for approximately 54% of the total study period.

The patients' global evaluations of treatment efficacy at the end of the study period (Fig. 1) demonstrated significant differential responses between the

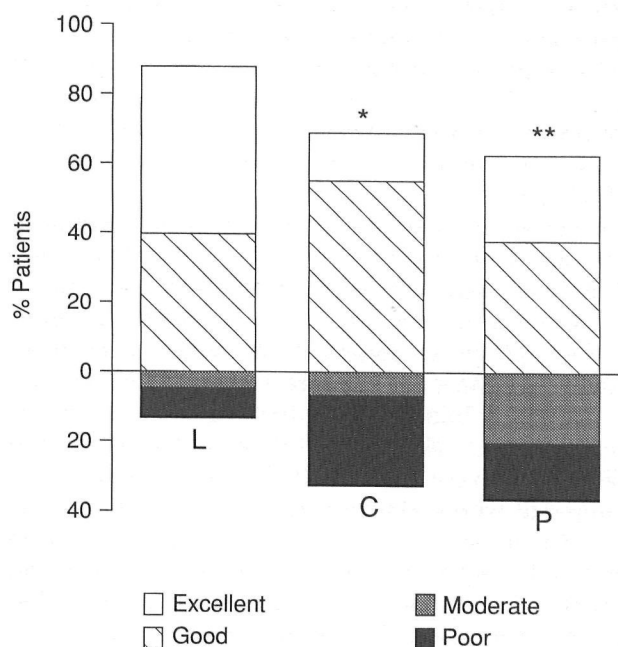


Fig. 1. Patients' global evaluation of therapeutic efficacy at end of trial; * $P < 0.05$, ** $P < 0.01$ (Mann-Whitney U-test). L = levocabastine; C = sodium cromoglycate; P = placebo.

three groups ($P = 0.04$). At the end of the study, 87% of levocabastine-treated patients considered therapeutic efficacy to be excellent or good, as compared with 68% of sodium cromoglycate-treated patients ($P = 0.006$) and 63% of those who received placebo ($P = 0.05$). There was no significant difference in

Table 1. Patient demographics

	Levocabastine	Sodium cromoglycate	Placebo
No. of patients in efficacy analysis (M/F)	28 (13/15)	32 (12/20)	29 (15/14)
No. of children (≤ 15 years)	5	3	5
Median age in years (range)	30 (7–66)	31 (10–69)	30 (13–61)
Median weight in kg (range)	69 (25–94)	66 (29–111)	67 (35–90)
Median duration of disease in years (range)	11 (2–40)	16 (3–60)	15 (2–45)
Base-line symptoms (mild/moderate/severe)*			
Ocular irritation	11 (8/2/1)	15 (9/4/2)	13 (10/2/1)
Photophobia	6 (5/1/0)	7 (4/1/2)	3 (3/0/0)
Red eyes	3 (3/0/0)	7 (4/1/2)	2 (2/0/0)
Lacrimation	3 (3/0/0)	8 (6/1/1)	7 (4/1/2)
Lid oedema	3 (3/0/0)	3 (2/0/1)	1 (1/0/0)
Conjunctival oedema	0 (0/0/0)	2 (2/0/0)	0 (0/0/0)
Nasal symptoms	13 (10/0/3)	17 (12/3/2)	10 (4/4/2)
Previously treated patients (total)	6	2	7
Hyposensitization	2	2	3
Medications	5	1	7
Hypersensitivity reactions** to:			
Grasses	25	30	28
Weeds	5	10	9
Trees	9	11	10
Other	3	2	1

* No. of patients.

** Positive skin prick or radioallergosorbent (RAST) test.

treatment efficacy between the sodium cromoglycate group and the placebo group. Similarly, the investigator rated treatment efficacy to be excellent or good in 91% of levocabastine patients, 68% of sodium cromoglycate-treated patients, and 68% of the placebo group. However, in this case, the intergroup differences were not significant.

Investigator assessments of symptom severity after 2 weeks of treatment and at the end of the study period revealed that symptom severity was consistently lower in the levocabastine group. Levocabastine provided significantly better relief from nasal symptoms than either sodium cromoglycate ($P < 0.01$) or placebo ($P < 0.01$) after 2 weeks of treatment. At the end of the trial, the intergroup differences were significant for levocabastine, as compared with sodium cromoglycate, for the severest ocular symptom ($P < 0.05$), for lacrimation ($P < 0.01$), and for red eyes ($P < 0.05$). There were no statistically significant intergroup differences between the sodium cromoglycate and placebo groups.

The AUC for severity of ocular symptoms was consistently lower in the levocabastine group. However, the intergroup differences did not reach statistical significance. In all, 37% of levocabastine-treated patients were virtually symptom-free ($VAS \leq 10$) for at least 75% of the study period, as compared with 6% of sodium cromoglycate-treated patients ($P < 0.01$) and 4% of those who received placebo ($P < 0.01$). The percentage of patients with mild to moderate symptoms ($VAS < 50$) for most of the study period was also higher in the levocabastine group than in either of the other groups; however, the intergroup differences did not reach statistical significance (Fig. 2).

Levocabastine provided significantly better symptomatic relief on high-pollen days than either of the other treatments (Fig. 3). In all, 33% of levocabastine patients were virtually symptom-free on such days, as opposed to 6% of the sodium cromoglycate-treated patients ($P = 0.02$) and 4% of those who received placebo ($P = 0.02$). This trend was also apparent on days when the pollen count was low; however, in this case, the intergroup differences did not attain statistical significance.

The use of rescue medication was consistently lower in the levocabastine group than in either of the other treatment groups; however, the intergroup differences did not reach statistical significance. Terfenadine was used by 57% of levocabastine patients at some point during the trial, as compared with 63% of sodium cromoglycate patients and 62% of patients in the placebo group. The mean number of terfenadine tablets consumed per patient during the trial was 2.4 in the levocabastine group, as compared with 4.1 in the sodium cromoglycate group and 3.0 in the placebo group. In addition, only 25% of le-

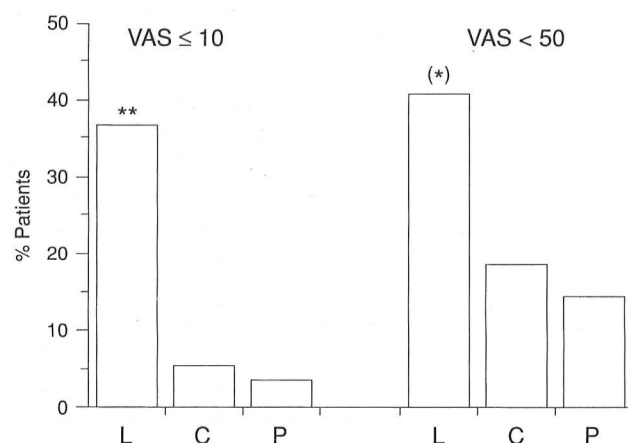


Fig. 2. Percentage of patients who were virtually symptom-free ($VAS \leq 10$) and who experienced only mild or moderate symptoms ($VAS < 50$) for at least 75% of the entire study period; ** $P < 0.01$ versus cromoglycate and versus placebo; (*) $0.05 < P < 0.1$ versus cromoglycate and versus placebo (Fisher's exact probability test). L = levocabastine; C = sodium cromoglycate; P = placebo.

vocabastine patients used nasal rescue medication at some point during the trial, as opposed to 41% of sodium cromoglycate patients and 31% of those in the placebo group.

A total of 44 patients reported adverse reactions during the course of the trial (11 in the levocabastine group, 18 in the sodium cromoglycate group, and 15 in the placebo group). The most frequent adverse reaction was ocular irritation after application of the study medication. This was reported by five levocabastine patients, five sodium cromoglycate patients, and eight patients in the placebo group. Headache was another common adverse effect, which was reported by three patients in the levocabastine group, as compared with seven patients in each of the other groups. A total of five patients withdrew from the trial because of adverse effects. Two levocabastine and two placebo patients withdrew as a result of ocular irritation, and another patient from the placebo group discontinued because of abdominal pain.

There were no significant intergroup differences in changes in body weight during the study period. Changes in clinical chemistry indicators during the study were random and comparable in all three treatment groups. At the end of the trial, levocabastine plasma concentrations were determined in a total of 27 patients. The mean plasma concentration of levocabastine was 0.66 ng/ml.

Discussion

The results of this trial demonstrate that topical levocabastine is significantly superior to both sodium cromoglycate and placebo eye-drops for the prophylaxis and treatment of seasonal allergic conjunctivitis. A total of 87% of levocabastine-treated patients

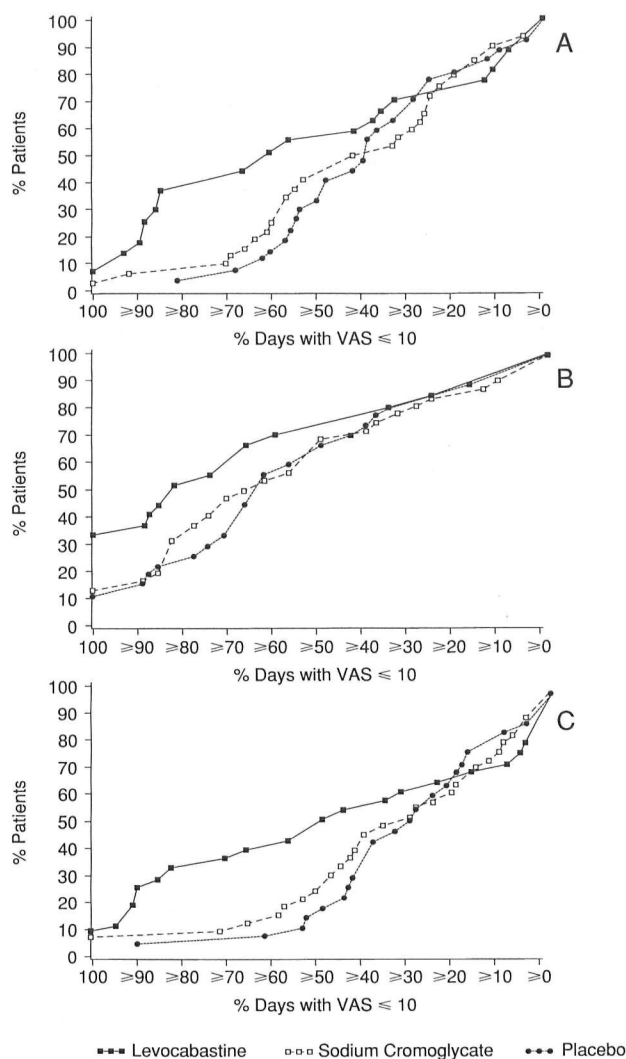


Fig. 3. Cumulative distributions of individual percentages of days with ocular VAS scores ≤ 10 (virtually symptom-free) during the entire study period (A); on days when pollen count was low (B); and on days when pollen count was high (C).

had an excellent or good response to treatment, as compared with 68% of sodium cromoglycate-treated patients and 63% of those who received placebo. In particular, the intensity of the severest ocular symptom was significantly lower in the levocabastine group than in the sodium cromoglycate group ($P < 0.05$) and in the placebo group. It is interesting to note that the therapeutic efficacy of sodium cromoglycate eye-drops was not significantly different from that of placebo eye-drops. This was probably due to the fact that any eye-drop, even placebo, provides a certain degree of symptomatic relief. Indeed, in this study the placebo response was particularly high. It is difficult to avoid this placebo effect for a number of reasons. Firstly, symptom severity constantly changes, depending on the pollen count, the time of day, and the amount of time the patient

spends outdoors. Secondly, in prophylactic studies such as this, periods of high-pollen counts may not be sufficient to allow symptoms to develop fully in all patients.

The superior efficacy of levocabastine was most apparent on days when the pollen count was high, when 33% of levocabastine patients were virtually symptom-free, as compared with only 6% of sodium cromoglycate ($P = 0.02$) and 4% of placebo patients ($P = 0.02$). A similar trend has been observed in other studies (2, 3).

Interestingly, despite the fact that less rescue medication (terfenadine and corticosteroid nasal spray) was used in the levocabastine group, the severity of nasal symptoms was significantly less in this group of patients than in either of the other groups ($P < 0.01$). The effect of the levocabastine eye-drops on nasal symptoms is probably the result of their passage through the lacrimal duct into the nose rather than a systemic effect of this agent, as the mean plasma concentration of the drug was too low (0.66 ng/ml) to account for any systemic effects.

Levocabastine eye-drops were well tolerated. The total incidence of adverse effects, and, in particular, the incidence of ocular irritation after application of the drug, was no greater in the levocabastine group than in the placebo group.

Conjunctival provocation tests have previously shown that topical levocabastine is more effective than sodium cromoglycate in preventing ocular allergic reactions. Moreover, a number of studies have shown that the two therapeutic approaches are equally effective in the treatment of allergic conjunctivitis (4, 8, 9, 13, 14). The present study, however, clearly demonstrates that topical levocabastine was significantly superior to sodium cromoglycate for the prophylaxis and treatment of this seasonal condition, supporting the results of another recent study (2).

In conclusion, topical levocabastine is more effective than sodium cromoglycate and placebo for the prophylaxis and treatment of seasonal allergic conjunctivitis. Moreover, levocabastine eye-drops are well tolerated by the vast majority of patients. It would, therefore, appear that topical levocabastine should be considered to be a primary local treatment option for the treatment of this condition.

References

1. ARMALY MF. Corticosteroid induced glaucoma. In: FRAUNFELDER FT, ROY TH, eds. Current ocular therapy. Philadelphia: WB Saunders, 1980: 444-5.
2. AZEVEDO M, CASTEL-BRANCO MG, FERRAZ OLIVEIRA J, RAMOS E, DELGADO L, ALMEIDA J. Double-blind comparison of levocabastine eye drops with sodium cromoglycate and placebo in the treatment of seasonal allergic conjunctivitis. Clin Exp Allergy 1991; 21: 689-94.
3. BENDE M, PIPKORN U. Topical levocabastine, a selective H_1

- antagonist in seasonal allergic rhinoconjunctivitis. *Allergy* 1987; 42: 512-15.
4. CIPRANDI G, ERQUETI PM, SACCA S, CILLI P, CARONICA GW. Levocabastine versus cromolyn sodium in the treatment of pollen-induced conjunctivitis. *Ann Allergy* 1990; 65: 156-8.
5. CRONIN TP. Cataracts with topical use of corticosteroids and idoxuridine. *Arch Ophthalmol* 1964; 72: 198.
6. DECHANT KL, GOA KL. Levocabastine. A review of its pharmacological properties and therapeutic potential as a topical antihistamine in allergic rhinitis and conjunctivitis. *Drugs* 1991; 41: 202-24.
7. KIRKEGAARD J, SECHER C, MYGIND N. Effect of the H₁-antihistamine chlorpheniramine maleate on histamine-induced symptoms in the human conjunctiva. *Allergy* 1982; 37: 203-8.
8. MÖLLER C. Levocabastine eye-drops in comparison with cromoglycate in the treatment of conjunctivitis in children with birch pollinosis. *Pediatr Allergy Immunol* 1990; 1: 87-9.
9. ODELAM H, BJÖRKSTÉN B, AFKLERCKER T, RIMÅS M, KJELLMAN N-IM, BLYCHERT L-O. Topical levocabastine versus sodium cromoglycate in allergic conjunctivitis. *Allergy* 1989; 44: 432-6.
10. RIMÅS M, KJELLMAN N-IM, BLYCHERT L-O, BJÖRKSTÉN B. Topical levocabastine protects better than sodium cromoglycate and placebo in conjunctival provocation tests. *Allergy* 1990; 45: 18-21.
11. STOKES TC, FEINBERG G. Rapid onset of levocabastine eye-drops in histamine-induced conjunctivitis. *Clin Exp Allergy* (submitted).
12. VANDEN BUSSCHE G. Levocabastine hydrochloride. *Drugs Future* 1986; 11: 10.
13. WIHL JÅ, RUDBLAD S, KJELLÉN H, BLYCHERT LA. Levocabastine eye-drops versus sodium cromoglycate in seasonal allergic conjunctivitis. *Clin Exp Allergy* 1991; 21 (Suppl. 2): 37-8.
14. ZAWODNIK S, PETITPIERRE M, DE WURSTEMBERGER B, GERBER M. La levocabastine dans le traitement de la conjonctivite allergique: une étude clinique en double insu. *Med Hyg* 1989; 47: 2021-4.

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