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Double-masked controlled clinical trial of 5% tolmetin versus 0·5% prednisolone versus 0·9% saline in acute endogenous nongranulomatous anterior uveitis

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SUMMARY A double-masked controlled clinical trial of 5% unpreserved tolmetin versus 0·5% prednisolone versus 0·9% saline in acute endogenous nongranulomatous anterior uveitis was carried out on 100 patients. 69% of the prednisolone-treated patients were judged 'cured' at the end of the 3-week study. This is compared with a cure rate of 47% for the tolmetin-treated patients and 53% for the placebo (saline) group. No statistically significant difference was established between the 3 groups.

1-methyl-5-p-toluoylpyrrole-2-acetic acid (tolmetin) is a nonsteroidal compound with antiprostaglandin property. It has been widely used in the treatment of rheumatic disorders, and its effects are well documented.[1,2] Tolmetin has had considerable anti-inflammatory activity when used topically in experimentally induced ocular inflammation in the rabbit (D. Gilbert, Smith and Nephew Ltd, personal communication), but its effectiveness in treating ocular inflammation in man has not been assessed. This trial was therefore designed to compare the efficacy of tolmetin with that of a widely used steroidal preparation, prednisolone disodium phosphate, and a placebo, saline, in the treatment of acute endogenous nongranulomatous unilateral anterior uveitis.

Patients and methods

The trial was conducted double-masked with unpreserved tolmetin 5% prednisolone (Predsol) 0·5%, and preserved sterile saline 0·9%. One hundred patients who presented consecutively in the Casualty Department of St Paul's Eye Hospital, Liverpool, during the period September 1980 to February 1981 with unilateral acute endogenous non-granulomatous anterior uveitis were referred to one of the 3 observers.

Pregnant women, patients under the age of 16, patients with one eye, and those on systemic or topical steroids were not included.

Consent having been obtained, each patient was assigned a trial number which randomly allocated him or her to one of the 3 treatment groups. Patients were instructed to instil the trial drops every 2 hours during the waking period and also atropine 1% drops once a day. At the first visit a full clinical history was taken, and the patient's symptoms, visual acuity, degree of ptosis, signs of inflammation, and intraocular pressure were assessed. The patient's symptoms and signs were scored on a 0–3 severity scale. Further assessments were carried out on days 3, 7, 14, and 21, and the frequency of treatment was accordingly adjusted.

The trial was concluded on day 21. When possible a given patient was assessed by the same observer throughout the study.

Patients judged to be getting worse or who developed bilateral disease were taken off the trial and treated as indicated.

Results

Six patients were excluded from analysis, 5 failed to reattend, and one developed bilateral disease. Thus 32 patients were allocated to prednisolone, 32 to tolmetin, and 30 to saline. In these treatment groups 8, 10, and 12 patients respectively were judged to have failed to respond within a 15-day period and had their treatment altered. The saline-treated group had the highest percentage of patients withdrawn as treat-

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ment failures during the trial at 3, 7, and 14 days, but by the end of the trial (day 21) the tolmetin-treated group had the highest percentage of patients classified as treatment failures (Table 1).

At the conclusion of the trial 22 patients who received prednisolone, 15 who received tolmetin, and 16 who received saline were judged cured. This gives a cure rate for prednisolone of 69%, tolmetin 47%, and saline 53%. The difference between the groups is not statistically significant.

All the treatment groups showed statistically significant improvement in total symptom scores at 3, 7, 14, and 21 days (Wilcoxon signed ranks test, $p<0{\cdot}025$). The prednisolone group showed statistically significant improvement in total clinical sign scores at 3, 7, 14, and 21 days, while the tolmetin group did not show a significant reduction in total sign scores until the 14th day, and the saline group showed a significant reduction only at 21 days.

When the overall scores, that is, symptoms and sign scores, were taken together (which determined whether the patient was judged cured or failed), no statistically significant difference was detected between the groups at 3, 7, 14, and 21 days, though the prednisolone-treated group of patients had the highest percentage of patients cured at all stages in the trial (Table 2).

Table 1 *Percentage treatment failures*

Treatment	*Day 3*	*Day 7*	*Day 14*	*Day 21*
Prednisolone	9%	22%	25%	31%
Tolmetin	13%	19%	31%	53%
Saline	23%	37%	40%	47%

Table 2 *Percentage cure rate*

Treatment	*Day 7*	*Day 14*	*Day 21*
Prednisolone	6%	31%	69%
Tolmetin	3%	19%	47%
Saline	3%	20%	53%

Discussion

Prostaglandins are naturally occurring substances

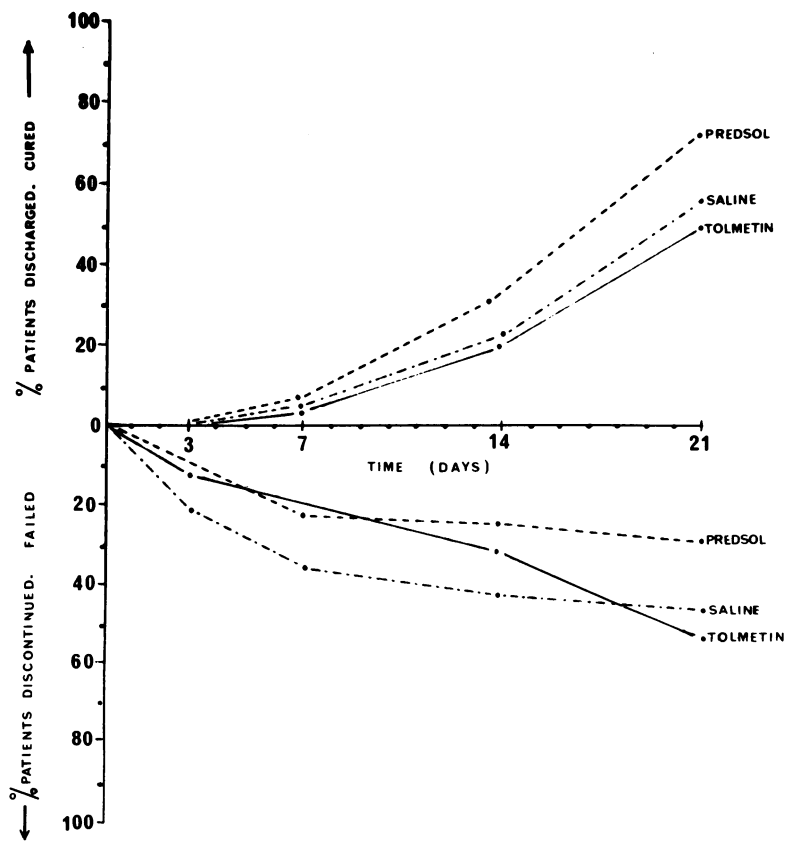

Fig. 1 *Patient progress through trial.*

which can be found in the conjunctiva and the anterior uvea.[3–6] Arachidonic acid and dihomo-y-linoleic acid are influenced by prostaglandin synthetase to form PGE and PGE_2 respectively, which appear to influence inflammation via cyclic AMP.[7] Irritation of the eye or the administration of arachidonic acid result in hyperaemia, miosis, breakdown of the blood aqueous barrier, ultrafiltration of macromolecules, and an increase in intraocular pressure. Similar effects can be seen in anterior uveitis.[7] The mode of action of nonsteroidal anti-inflammatory compounds is thought to be by the inhibition of prostaglandin synthetase. Various classes of prostaglandin inhibitors have been used in the treatment of uveitis, for example, aspirin, oxyphenbutazone, steroids.[8–12] Tolmetin is a potent inhibitor of prostaglandin synthetase, acting in a competitive reversible manner, and ranks with indomethacin in vitro in this respect.[13] Steroids are poor inhibitors of prostaglandin synthetase, and their usefulness is limited in the treatment of acute ocular inflammation by their potential side effects, namely, potentiation of viral, bacterial, and fungal infection[14–16] and an unpredicatable rise in intraocular pressure in steroid responders.[17–19]

In this series the reduction in symptom scores in all 3 groups can be attributed to atropine drops and or the spontaneous behaviour of the disease.

Clinical sign scores at day 14 of the trial showed tolmetin to be somewhat quicker than saline but took longer than prednisolone to become statistically significant. However, on completion of the trial period 47% of tolmetin-treated patients, 53% of saline-treated patients, and 69% of prednisolone-treated patients were judged to be cured (Fig. 1). No statistically significant difference could be determined between the 3 groups.

Thus the efficacy of tolmetin and steroids in treating nongranulomatous anterior uveitis in man does not appear to be similar to that reported when it was used in the treatment of experimentally induced uveitis in rabbits (D. Gilbert, personal communication).

The fact that 50% of the placebo-treated patients were deemed cured at 21 days is further evidence that nongranulomatous anterior uveitis is a self-limiting disease.[20] Unfortunately it is not at present possible to predict which cases will terminate spontaneously, so all must be treated initially.

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