A Double-Blind Study of the Efficacy of Topical Ketorolac Tromethamine Gel in the Treatment of Ankle Sprain, in Comparison to Placebo and Etofenamate

Wilfred Diebschlag, Wolfgang Nocker, and Roy Bullingham

In a double-blind, placebo-controlled study the efficacy and safety of topical ketorolac tromethamine were assessed in the reduction of inflammation and pain due to ankle sprain. Ketorolac 2% gel was compared with etofenamate and placebo (ketorolac vehicle) in a 15-day study. Patients attended for visits on days 1 (admission), 2, 3, 4, 8, and 15 of the study. Measurements of efficacy were ankle volume, pain measured on visual analogue scales (VAS) and verbal rating of pain. Safety was assessed by volunteered adverse events and vital signs. A total of 37 patients was admitted to the study of whom 13 received ketorolac, 12 placebo, and 12 etofenamate. One patient receiving ketorolac was lost to follow-up on day 15 owing to an unrelated accident. The remaining 36 patients completed the study. Ketorolac was significantly better than placebo in reducing the volume of the injured ankle based on the maximum, the area under the curve, and the day 15 percentage changes in ankle volume. Results for etofenamate were similar to those for ketorolac for all three variables and there were no significant differences between the active treatments. Reductions in VAS pain at rest were more marked in the ketorolac group than either of the other groups at all visits. On day 4 the differences between ketorolac and each of the other groups were statistically significant. Reductions in VAS pain on movement were also greatest for the ketorolac group at all visits. The differences between ketorolac and each of the other groups achieved statistical significance on days 4 and 8, but were marginal in terms of significance on day 2. The incidence of VAS pain at night was lower for ketorolac than for either of the other groups, but only the difference from placebo achieved statistical significance. There were greater improvements in verbal ratings of pain severity for ketorolac than for placebo. This difference was statistically significant on day 4. Results for the two active treatments were slightly in favor of ketorolac, but differences were not statistically significant. Mean plasma concentrations of ketorolac were 0.183 μg/ml on day 4, and 0.170 μg/ml on day 15. Only two minor adverse events were reported, one each for ketorolac and etofenamate, and no important changes occurred in any of the vital sign measurements. The results of this small scale study of the topical application of ketorolac gel are encouraging. A good effect in the early relief of pain and reduction in ankle swelling, with few side-effects, occurs at plasma ketorolac concentrations not inconsistent with one local effect.

Ketorolac tromethamine (hereafter referred to as ketorolac) is a prostaglandin synthetase inhibitor that displays potent analgesic, anti-inflammatory and antipyretic properties in animal models. It has been studied clinically to establish its efficacy and safety as an analgesic in postoperative and cancer pain, in oral and injectable formulations, and has shown high analgesic potency (with 10 mg ketorolac orally or intramuscularly being equivalent to 10 mg intramuscular morphine).

A topical formulation of ketorolac is now under development for the treatment of musculoskeletal injuries. A human bioavailability study indicated

From the Institut fur Arbeitsphysiologie, Technical University Munich, Munich, West Germany (Drs. Diebschlag and Nocker), and Syntex Research–Europe, Maidenhead, Berkshire, United Kingdom (Dr. Bullingham). Address for reprints: Prof. Dr. med. W. Diebschlag, Institut fur Arbeitsphysiologie, Technical University Munich, Barbara Strasse 16, D-8000 Munich 40, West Germany.

high systemic absorption of ketorolac was possible from topical administration, and a 5% concentration could give plasma ketorolac concentrations in the range achieved during therapy with the oral and injectable formulation. Skin reactions were infrequent.

The present study was carried out to investigate the efficacy of topical ketorolac in reducing the swelling and pain of ankle sprain. Although when administered systemically in analgesic doses of 10 mg to 30 mg ketorolac does not display significant clinical anti-inflammatory activity, higher doses may show such activity.

Following topical administration the possibility existed that the local concentration of ketorolac could be higher than the systemic concentration and be sufficient to provide a reduction in swelling. Therefore, swelling was measured using a precise plethysmographic méthod, as well as pain using visual analogue and verbal rating scales.

PATIENTS AND METHODS

The study was of randomized double-blind parallel group design, with three groups comprising test medication, active and placebo controls. Five percent etofenamate gel, (a standard topical therapy in Germany by Tropon Ltd., Cologne), was chosen as the active control. Ketorolac was formulated in 2% concentration as a gel.

Patients with acute unilateral untreated ankle sprain were entered, and applied the assigned medication topically three times daily for 14 days without occlusion. During this time, reported pain was recorded and volumetric assessments of the injured relative to the uninjured limb were made by an established methodology using water displacement.[1-7] Blood was taken from all patients and plasma ketorolac concentration subsequently measured in those who had been assigned ketorolac, as an indication of the extent of percutaneous absorption.

Male and female patients, aged between 18 and 50 years, and having a measured or estimated weight of 45 to 100 kg, were admitted if suffering from acute ankle sprain. The injury (to either ankle) was to be of slight or moderate severity and presenting to the investigators within 24 hours of occurrence. Severe ankle sprains with torn ligaments were excluded by X-ray. Patients were to have good general health and women of child-bearing potential were excluded. Skin disease that was either local to the site of application or of generalized etiology was also a contraindication to admission.

Patients were not to have received previous therapy for their ankle sprain and must not have been receiving regular doses of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Similarly, intermittent or intercurrent medical conditions requiring the use of NSAID preparations were also excluded.

Twelve patients per group were to be recruited, this being a sample size with which etofenamate and other active topical preparations had been statistically distinguished from placebo in previous studies.

Study medication was supplied in 3 g quantities dispensed in 5 g-sized tubes. The whole contents of one tube were to be applied, without occlusion, at each application. Medication was to be applied three times a day (9 g total per day) in the morning, at midday, and in the evening, each day for 14 days. Treatment assignment was block-randomized, and medication sets were sequentially numbered and of identical appearance. Medication assignment for each medication set was supplied in a sealed envelope which was only to be opened if a serious patient event necessitating treatment disclosure had occurred, but didn't in any case.

Oral paracetamol was supplied, to be used as additional medication if insufficient relief was given by application of the trial medication. Patients were carefully instructed to use this concomitant medication only if insufficient relief was provided by proper regular application of the trial medication. Excessive use was discouraged. Patients were required to bring back the supplied paracetamol at the 1-week and last visits. At each of these visits the paracetamol consumption (if any) since the previous visit was recorded and the remaining tablets counted as a check on compliance.

No other analgesic or anti-inflammatory medication was permitted during the study. Patients were particularly advised about the use of proprietary cough/cold mixtures and over-the-counter analgesics. Any other concomitant medication used by the patients, including any drugs being used for other indications, was fully documented.

Patients were instructed not to use ice packs or other local forms of self applied therapy at home. Physiotherapy was not given.

At admission (day 1), following confirmation of the patient's eligibility to enter the study, verbal informed consent was obtained from the patient for study entry. The patient was then assigned the next sequentially numbered medication set. A physical examination was carried out, including vital signs, and demographic information and full details of the ankle injury and of its time of occurrence were recorded. The pain of the injury was assessed using verbal rating and visual analogue scales for pain intensity, and then the volume of both the injured and

the uninjured limb were measured using a water displacement method. The first treatment was then applied in the clinic as the whole of the contents of one tube, and a nonocclusive bandage was applied avoiding compression. Patients were instructed in the method of applying the treatment and bandage. The paracetamol supply was issued with detailed instructions for use.

On each of the following days (2, 3, 4, 8, and 15) the patients attended for assessment of pain (using the verbal rating and visual analogue scales) and volumetric measurement of the lower limbs. Volumetric measurements were carried out at approximately the same time of day for each patient to avoid known diurnal fluctuations in limb volume. Vital signs were recorded before the volumetric measurement. Assessments were carried out before the morning application of treatment. The patients were asked if anything else was bothering them, and reported symptoms recorded. The skin on the treated ankle was examined for signs of irritation, and the appearance recorded (no, mild, moderate, or severe reaction). Paracetamol use (if any) was noted for the preceding period. Checks on other concomitant medication were made.

On day 4 and day 15 a venous blood sample was withdrawn, centrifuged, and the plasma stored frozen for later analysis of ketorolac concentration in those assigned ketorolac.

On day 8 and day 15, the patient was asked to bring back the supplied paracetamol so that a tablet count could be performed.

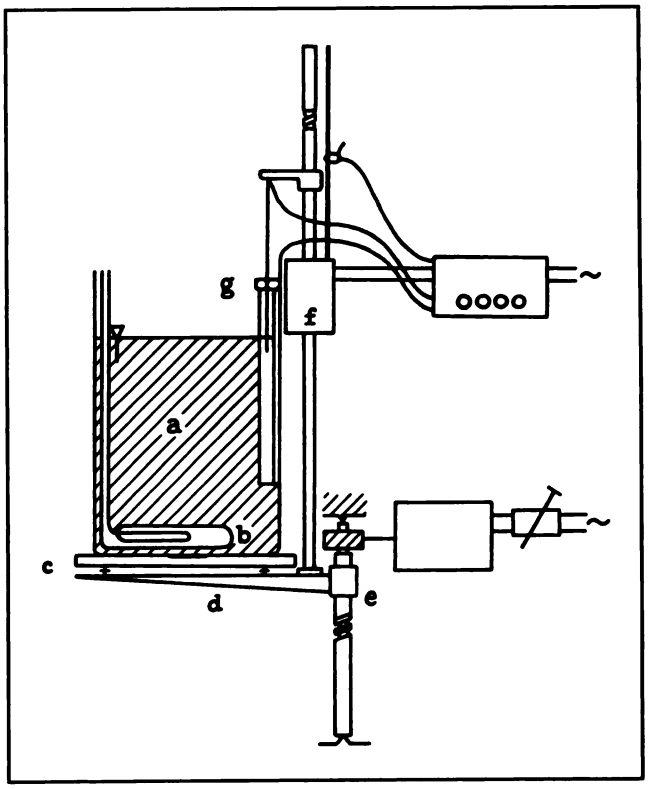

Figure 1. Equipment for volumetric measurement of ankle volume. a: water-filled glass vessel; b: heating coils; c: three-point supported cast steel plate; d: lifting platform; e: spindle for moving the steel plate; f: stepping motor; g: measurement sensor.

Assessment Procedures

Pain Intensity. Pain was assessed using three 100 mm horizontal, unmarked visual analogue scales (VAS) labelled at left and right with "no pain" and "severe pain," respectively. The three VAS were to refer to pain at rest, pain on movement, and pain at night. The scales were marked at each visit, without reference to previously marked scales. The average pain intensity over the last 24 hours was also assessed on a four-point verbal rating scale as: 0 = none; 1 = mild; 2 = moderate; 3 = severe.

Measurement of Ankle Volume. The measurement of ankle volume was made by determining the amount of water displaced by the leg. The equipment (Figure 1) has been described in detail previously.[2] The limb was placed into a vessel containing water whose temperature was thermostatically controlled at 30°C. Both before and after placing the limb in the vessel the water level was measured electronically by electrically lowering a measuring pin with a stepping motor until it touched the surface of the water. A small voltage was applied between the pin and electrode inserted into the container, so that when the circuit was completed via the water, the pulse motor was cut off and stopped the pulse counter. The pulses were then converted electronically from a prior calibration into a displaced volume. To ensure that the lower limbs of the patient were always immersed in the water bath to the same depth, the skin at the level of the head of the fibula was indelibly marked by tattooing with India ink on both limbs. To compensate for measurement errors, the average value of two measurements on each limb was used for the evaluation. All measurements were carried out at about 0900 hours, in an air-conditioned room. The patients remained in the room for a period of adaptation before the measurements were made.

Plasma Ketorolac Concentration. Plasma ketorolac was determined by a specific high performance liquid chromatography method.

Statistical Methods

In order to preserve the 5% level for significance testing and avoid the use of multiple comparison procedures, formal statistical significance tests were carried out for just two of the three possible treatment differences. The two major comparisons of interest were considered to be between ketorolac and placebo, and between ketorolac and etofenamate. As it was not an objective of the study to establish the efficacy of etofenamate, the third comparison was not tested. All statistical significance tests performed were therefore carried out at the 5% level and were two-sided.

The analysis of ankle volume followed the method described by Diebschlag.[2] For the injured and uninjured ankles separately, the mean of the two duplicate measurements was calculated at each visit for each patient. A corrected volume was then calculated for the injured ankle on the assumption that physiological fluctuations in volume affect both ankles equally. The correction involved subtracting from the injured ankle volume at a visit the change in uninjured ankle volume between that visit and admission. See Table I for an example of this; corrected injured ankle volumes are expressed as percentage increases or decreases in comparison with the injured ankle volume at the admission visit.

Three variables were used to summarize these percentage changes in corrected ankle volume over the treatment period: the maximum, the area under the curve (AUC), and the end of study volume (day 15). The maximum change was the largest increase in corrected ankle volume for patients who experienced such an increase. For those who did not the maximum change was the smallest decrease.

The AUC was calculated using the trapezoidal rule. Resulting values were normalized by dividing by the total time involved (14 days). Thus the AUC represents a percentage change in corrected volume averaged over the study period. Each of these summary variables was analyzed using a one-way analysis of variance with treatment as the factor. Due to departures from normality of the distributions involved, all were repeated using the Mann-Whitney U test. A further analysis was performed in order to confirm the results. To eliminate the effects of the imbalance at admission in the difference between injured and uninjured ankle volume, this difference at subsequent visits was expressed as a percentage of the admission value. Treatment differences were then tested using the Mann-Whitney U test.

For the Visual Analogue Scale (VAS) of pain at rest and on movement, absolute changes in comparison with the entry value were calculated for each patient at each visit. As pain was expected to last only for a few days, treatment comparisons were made after 2, 4, and 8 days of treatment. Differences between treatments were then tested using the Mann-Whitney U test. The analyses were repeated using percentage instead of absolute changes for measurements made at admission to the study in order to confirm the results. The incidence of pain at night scored on the VAS was low after the admission visit, and was therefore analyzed by examining the incidence at any visit during the treatment period based on all patients admitted to the study regardless of whether night pain was recorded at admission. Treatment differences were tested using Fisher's Exact Test.

Pain severity on the verbal rating was summarized at each visit. Patients were also classified as the "same," "better," or "worse" than at admission according to their pain severity, and treatment differences for these changes in severity were tested on days 2, 4, and 8. Due to the low incidence of the category "worse," this category was grouped together with the "same," and differences analyzed using Fisher's Exact Test. The number of patients who used paracetamol was small, and so no formal statistical analysis was performed. Plasma levels of ketorolac in the ketorolac treatment were summarized.

Adverse events were of very low incidence and are reported but not statistically analyzed.

TABLE I

Analysis of Ankle Volume

Extremity	Vol. (ml) Day 1	Vol. (ml) Day 2	Vol. Change	Corr. Vol. Change (%) (Effect of Medication)
Injured	3216	3206	−0.3	−0.5
Uninjured	3132	3138	+0.2	—

RESULTS

A total of 37 patients was entered into the study of whom 13 received ketorolac and 12 each received etofenamate or placebo. One female patient receiving ketorolac failed to attend the last follow-up visit because of an unrelated motorcycle accident, and was replaced. Twelve patients in each group thus completed all visits. Table II summarizes demographic data and details of the injury for all patients admitted to the study. There were no torn ligaments

TABLE II

Demographic Data and Details of Injury

	2% Ketorolac	Placebo	Etofenamate
Number of patients:	13	12	12
Age (years):			
Mean	27	28	28
SD	6.1	5.3	3.6
Range	22–46	21–37	24–34
Sex:			
Male	8 (62%)	8 (67%)	8 (67%)
Female	5 (38%)	4 (33%)	4 (33%)
Weight (kg):			
Mean	71	70	71
SD	10.9	9.3	7.7
Range	58–98	56–83	60–62
Height (cm):			
Mean	174	173	174
SD	7.3	5.4	4.8
Range	163–184	167–185	166–181
Details of accident:			
Sports accident	10 (77%)	8 (67%)	8 (67%)
Fell on stairs	2 (15%)	1 (8%)	2 (17%)
Other	1 (8%)	3 (25%)	2 (17%)
Admission difference between injured and uninjured ankle volumes (ml):			
Mean	81.5	74.1	76.0
SD	9.7	6.5	10.2
Range	67–102	63–84	58.5–93.5

revealed by X-ray and no patients had self-administered any form of therapy. None of the patients reported any coexistent medical disorders. Apart from oral contraceptives none of the patients were taking any concomitant medication at admission to the study.

Ankle Volume

The mean injured ankle volumes at admission were nearly equal in all groups, being 3191, 3182, and 3186 ml for the ketorolac, placebo, and etofenamate groups, respectively. It can be seen from Figure 2 that an increase in mean ankle volume took place on day 2 in all three treatment groups, but this increase was much greater for the placebo group. On day 3

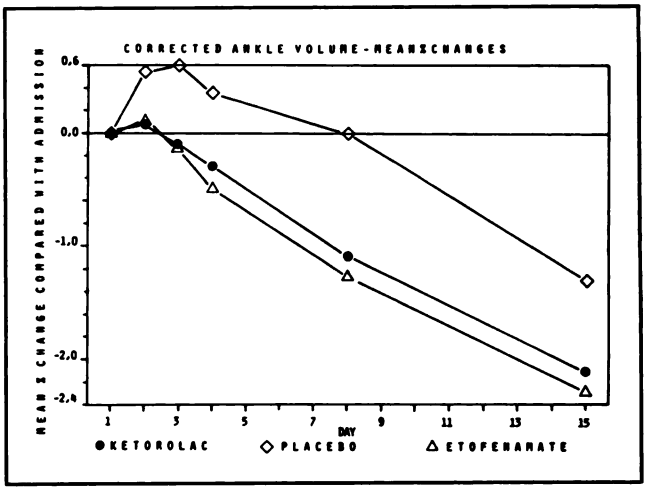

Figure 2. Corrected ankle volume—mean percentage change.

there was a further increase for the placebo group compared with decreases in the active treatment groups. From day 4 to the end of the study treatment differences in volumes were fairly constant.

The biggest decreases were seen in the etofenamate and ketorolac groups compared with much smaller decreases in the placebo group. Treatment group means for maximum percentage changes in ankle volume were 0.08%, 0.81%, and 0.11% in the ketorolac, placebo, and etofenamate groups, respectively. The difference of 0.72% between ketorolac and placebo in favor of ketorolac was highly statistically significant ($P = .002$). The small difference between etofenamate and ketorolac of 0.02% was not close to statistical significance (Table III).

The analyses of AUC and day 15 percentage changes show similar results to those seen for the maximum percentage changes. Treatment group means for the AUC percentage decreases in corrected ankle volume were 1.01%, 0.17%, and 1.14% in the ketorolac, placebo, and etofenamate groups, respectively. The treatment difference of 0.84% between ketorolac and placebo in favor of ketorolac was highly statistically significant ($P = .0001$); however, the difference between etofenamate and ketorolac of 0.13% was not close to statistical significance. Mean decreases in corrected ankle volume on day 15 were 2.13%, 1.32%, and 2.26% in the ketorolac, placebo, and etofenamate groups, respectively. The difference of 0.82% between ketorolac and placebo in favor of ketorolac was highly statistically significant ($P = .0001$). The difference between etofenamate and ketorolac of 0.13% was not close to statistical significance (Table III).

TABLE III

Percentage Changes in Corrected Ankle Volume: Summary of Statistical Analysis

		Treatment Difference	95% Confidence Interval	Statistical Significance
Maximum percentage change	Ketorolac minus placebo	−0.72	−1.16–−0.28	$P = .002$
	Ketorolac minus etofenamate	−0.02	−0.46–0.42	$P = .92$
AUC percentage change	Ketorolac minus placebo	−0.84	−1.17–−0.51	$P = .0001$
	Ketorolac minus etofenamate	0.13	−0.20–0.46	$P = .44$
Day 15 percentage change	Ketorolac minus placebo	−0.82	−1.02–−0.61	$P = .0001$
	Ketorolac minus etofenamate	0.13	−0.08–0.33	$P = .22$

Pain Assessments

VAS pain at rest, on movement, at night, and verbal rating of pain were analyzed. Values at admission were comparable between the groups although there was some tendency for the scores to be higher in the ketorolac groups, consistent with the somewhat larger difference in ankle volume.

Median values of pain at rest as recorded on a 100 mm VAS for each visit are shown graphically in Figure 3 for the patients who completed the study. Median measurements at admission were 25, 25, and 20 mm for the ketorolac, placebo, and etofenamate groups, respectively. The median had decreased to zero (no pain) by day 3 in the ketorolac group, by day 4 in the etofenamate group, but not until day 8 in the placebo group.

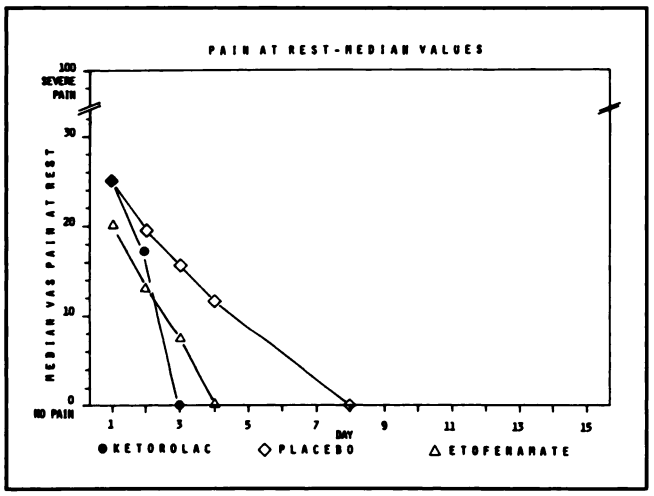

Figure 3. Pain at rest—median values.

For days 8 and 15 all patients were recording zero on the scale for pain at rest. On day 4, the median decreases in pain at rest were 25 mm (ketorolac), 12 mm (placebo), and 18 mm (etofenamate). The reduction in pain in the ketorolac group was statistically significantly greater than for placebo ($P = .003$) and for etofenamate ($P = .015$).

Median values of the VAS for pain on movement are shown graphically in Figure 4 for the 36 patients who completed the study. Median pain ratings at admission were 66, 61, and 56 mm for the ketorolac, placebo, and etofenamate groups, respectively, but was still 18 mm on day 15 for the placebo group. Compared with the admission visit, there were median decreases on day 2 in pain of 11, 8, and 5 mm in the ketorolac, placebo, and etofenamate groups, respectively. The advantage of ketorolac over the other two groups was marginal in terms of statistical significance ($P = .056$ for placebo and $P = .050$ for etofenamate). On day 4 the median decreases were 32, 16, and 21 mm for the ketorolac, placebo, and etofenamate groups, respectively. The reduction in pain in the ketorolac group was greater than that for placebo ($P = .0001$) or for etofenamate ($P = .004$). On day 8 the median decreases were 48, 25, and 32 mm for ketorolac, placebo, and etofenamate, respectively. The reduction in pain in the ketorolac group was greater than that for placebo ($P = .0001$) and for etofenamate ($P = .001$). The analysis of percentage changes produced significance levels that were similar to those described, the most important difference being that the advantage for ketorolac over etofenamate on day 2 narrowly ceased to be statistically significant ($P = 0.061$).

At admission 11/13 patients receiving ketorolac, 9/12 receiving placebo and 9/12 receiving etofenamate recorded any pain at night on the VAS. By the

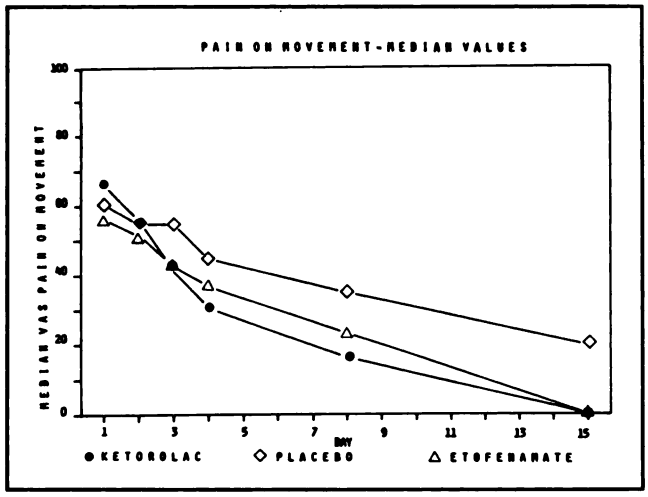

Figure 4. Pain on movement—median values.

second day the incidence had reduced to 7/13, 7/12 and 4/12 respectively. No further night pain was reported after day 2 in the ketorolac group, day 3 for etofenamate and day 4 for placebo. The lower overall incidence of pain at night in the ketorolac group compared with placebo achieved statistical significance ($P = .011$), but the difference between the two active treatments was not statistically significant.

The percentage of patients with an improvement in severity of pain is shown in Figure 5. It can be seen that by day 3 none of the patients receiving placebo had improved, compared with 11/13 receiving ketorolac and 6/12 receiving etofenamate. A similar magnitude of treatment difference was seen

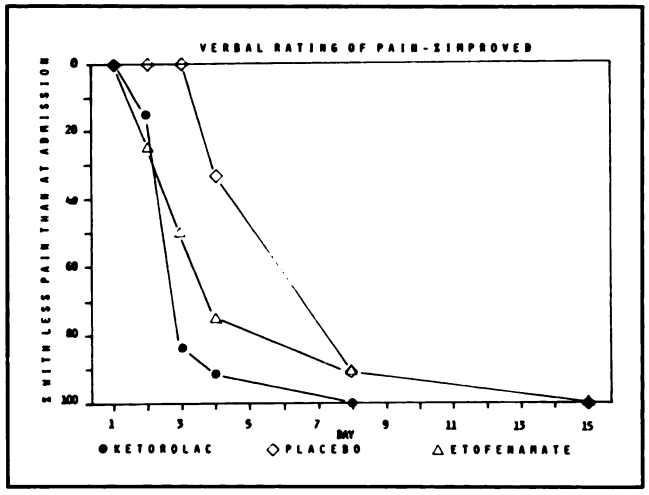

Figure 5. Verbal rating of pain—percent of patients improved.

on the fourth day, but the gap narrowed after day 4 and by the end of the study all patients had shown some improvement.

There were no statistically significant treatment differences for changes in verbal pain ratings on days 2 or 8. However, on day 4 the number of ketorolac patients with an improvement was statistically significantly greater than for those receiving placebo ($P = .004$). The difference between ketorolac and etofenamate was numerically in favor of ketorolac but did not achieve statistical significance.

Paracetamol Consumption

Two patients in each of the placebo and etofenamate groups and one in the ketorolac group took paracetamol during the study. Each patient took just two tablets on day 2, except for one patient in the placebo group who also took two tablets on day 3.

Plasma Ketorolac Concentration

Blood was collected from 11 patients in the ketorolac group on days 4 and 15 of the study for the measurement of plasma concentrations of ketorolac. Results are summarized in Table IV. On day 4 plasma ketorolac concentration ranged from 0.023 μg/ml to 0.815 μg/ml, with a mean of 0.183 μg/ml. On day 15 levels remained similar, with values ranging from 0.028 μg/ml to 0.402 μg/ml and a mean of 0.170 μg/ml.

Adverse Events

Only two adverse reactions were reported during the study. Patient 116, receiving ketorolac, reported a "yellow change of color in the injured area" on day 15. The severity of this reaction was rated as mild and of unknown relationship to the test medication. The reaction was of 6 days' duration but disappeared

TABLE IV

Plasma Concentration of Ketorolac (μg/ml) in Ketorolac Treatment Group

	Day 4	Day 15	Difference Between Day 15 and Day 4
Number of patients	11	11	11
Mean	0.183	0.170	−0.013
SEM	0.071	0.037	0.048
Minimum	0.023	0.028	−0.413
Maximum	0.815	0.402	0.251

after termination of treatment. The other adverse reaction was also reported on day 15 of the study. Patient 101, receiving etofenamate, reported "itching in the treated area." The severity of this reaction was rated as moderate and of probable relationship to the test medication. The reaction had been of 7 days' duration and continued for a further 3 days after the end of the study. No important changes in vital signs were observed for any medication.

DISCUSSION

Two measures, pain relief and antiphlogistic effect, were examined in this study to assess the efficacy of topically applied ketorolac. Etofenamate was also included as a positive control, since its effects have been well studied, it has been distinguished from placebo in a number of studies, and it has an established place in the topical therapy of sprains in Germany.

Ketorolac gel was found to be statistically superior to placebo for both reduction of pain on days 4 and 8 and for reduction of swelling overall and on day 15. Ketorolac was not distinguished from etofenamate, but was statistically superior to the latter on days 4 and 8 for the reduction in swelling and for pain on movement.

Plasma ketorolac concentrations were measured on days 4 and 15 in the group who had received ketorolac, to give an indication as to whether these results were achieved by systemic concentrations of the drug or by a local effect. On both days the concentrations had a mean value of about 0.2 μg/ml. The similarity of the plasma ketorolac concentrations on the two days suggests steady-state conditions had been reached by day 4. Sampling was done before the first dose of the morning, and therefore some 10 to 12 hours since the last application of ketorolac. Bioavailability studies of the topically applied gel give rather variable but often rather late peak concentrations so that the sampling time was unlikely to represent a trough concentration. Following a single oral 10 mg dose of ketorolac, the maximum plasma drug concentration averages about 0.9 μg/ml, appreciably more than the steady-state concentrations recorded here after multiple topical dosing. This result can be taken as some support for a local component of action from topical application, but is tentative without better definition of the plasma concentration/time profile for multiple topical dosing. Moreover, the occasional patient showed a plasma concentration within the therapeutic range following oral dosing.

Reported adverse complaints were minimal, consisting of one each for ketorolac and etofenamate. For the former, the report was of discoloration at the site of application, with an uncertain relation to drug therapy. For the latter, local pruritus was reported and considered as probably related to drug application. Again, although the numbers are small, the absence of complaints for ketorolac of significant localized reactions (especially of an irritative or allergic type) is encouraging. No systemic complaints were noted.

Overall, this small study shows topical application of ketorolac would seem to show excellent efficacy with few side-effects. The results need confirmation in larger patient groups, and further studies should be done to explore the possibility of a true topical effect.

This study was supported with a grant from Syntex Research.

REFERENCES

1. Diebschlag W: Eine einfache Apparatur zur Bestimmung des Fußvolumens und dessen Anderungen. *Z Ges Exp Med* 1970;152:179–185.

2. Diebschlag W: Neue Methode für genaue Messungen der Anderung des Extremitätenvolumens zur Quantifizierung eines Therapieerfolges bei verschiedenen Angiopathien. *Arzneim Forsch/Drug Res* 1975;25:438–439.

3. Diebschlag W: Benzydamine cream in post-traumatic oedema. *Int J Tissue Reactions* 1985;7:219–223.

4. Diebschlag W: O Diclofenaco Dietilamonio no tratamento do edema de articulacao do tornozelo causado por entroses. *A Folha Medica* 1988;96:403–408.

5. Diebschlag W, Nocker W: Einfluß einer topischen Behandlung auf den Krankheitsverlauf bei Sprunggelenks-Distorsionen. *Arzneim Forsch/Drug Res* 1987;37:1076–1081.

6. Diebschlag W, Nocker W: Behandlung akuter lateraler Sprunggelenksdistorsionen. *Munchner Med Wschr* 1987; 129(44):57/803–806.

7. Nocker W, Diebschlag W: Dosis-Wirkungsstudie mit O-(Beta-Hydroxyäthyl)-rutosid-Trinklösungen. *VASA* 1987;16:365–369.