Comparison of Ketoprofen, Piroxicam, and Diclofenac Gels in the Treatment of Acute Soft-Tissue Injury in General Practice

Rajni K. Patel, MRCS, MRCGP,[1] and Peter F. Leswell, CBiol, MIBiol,[2] on behalf of the General Practice Study Group

[1]Garrison Medical Centre, Woolwich, London, and [2]Clinical Research, Rhône-Poulenc Rorer (UK) Ltd., Eastbourne, East Sussex, United Kingdom

ABSTRACT

The efficacy, tolerability, and acceptability of topical applications of ketoprofen gel (2.5% w/w), piroxicam gel (0.5% w/w), and diclofenac gel (1% w/w), when administered three times daily for 5 days, in the treatment of acute (within 48 hours) soft-tissue injury, were compared in an open-label, randomized, multicenter, general practice study. Of 1575 patients recruited, 1048 received ketoprofen gel (525 used the gel with a dose-measuring device), 263 received piroxicam gel, and 264 received diclofenac gel. Ketoprofen gel was significantly superior to piroxicam gel in terms of global assessment of treatment response (improvement in 74% vs 65% of patients) and the severity of the injury (38% vs 26% "greatly improved") and in improvements in stiffness (71% vs 64%), restriction of mobility (34% vs 22%), and pain on pressure (81% vs 78%) and movement (83% vs 77%). Ketoprofen gel also compared favorably with diclofenac gel, with a larger proportion of patients assessing a great improvement in the injury (38% vs 30%). Patient acceptability of ketoprofen gel was significantly better than piroxicam gel. More patients noted a significant cooling effect with ketoprofen gel (71%) than with either piroxicam gel (49%) or diclofenac gel (60%). Ketoprofen gel also showed excellent tolerability. In conclusion, ketoprofen gel may offer benefits over established therapies for the treatment of acute soft-tissue injury.

INTRODUCTION

Acute soft-tissue injury is a common reason for general practice consultation.[1] Treatment usually involves topical application of agents with combined anti-

0149-2918/96/$3.50

inflammatory and analgesic properties. Although the currently available treatments have been shown to be effective and well tolerated, an alternative treatment, with improved patient acceptability as compared with established therapy, would be of obvious benefit.

Ketoprofen is a potent nonsteroidal, anti-inflammatory drug (NSAID) with excellent analgesic properties. Extensive clinical experience has demonstrated the efficacy and safety of ketoprofen, when administered either orally or parenterally, in a wide range of inflammatory and musculoskeletal disorders such as osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, lumbago, sciatica, renal colic, and postoperative pain.[2]

More recently, topical formulations have been developed for the treatment of acute minor musculoskeletal injuries, such as sports injuries, sprains, and strains. These formulations offer several advantages: rapid penetration, significantly greater elimination half-life (17 to 27 hours),[3] high joint tissue:plasma concentration ratios resulting in a prolonged local therapeutic effect,[4,5] and avoidance of undesirable systemic side effects. Several placebo-controlled studies have confirmed the efficacy and local tolerability of ketoprofen gel in the treatment of minor sports injuries[6] and acute low back pain.[4,5]

The aim of this study was to compare the efficacy, tolerability, and acceptability of treatment of ketoprofen gel with two other established therapies (piroxicam gel and diclofenac gel) in the treatment of acute soft-tissue injury in general practice. Additionally, the possible benefit of a dose-measuring device as an aid to application and patient compliance was investigated in one group of patients randomized to treatment with ketoprofen gel.

PATIENTS AND METHODS

This was an open-label, comparative, parallel-group, multicenter, general practice study comparing the efficacy, tolerability, and acceptability of treatment of ketoprofen gel (applied with or without a measuring device) with piroxicam gel or diclofenac gel in patients with acute (ie, generally within 48 hours) soft-tissue injury. Patients were excluded if they presented with any of the following: muscular or neurologic disorders liable to interfere with the study assessments; active arthritis in the affected limb; open wounds, infected skin, or fractures; underlying dermatitis or dermatosis associated with the injury; serious injuries requiring additional therapy (eg, physiotherapy other than ice/compression/elevation [ICE] treatment, topical steroid injection, or supportive bandaging); known hypersensitivity or allergy to aspirin or other NSAIDs, propylene glycol, or isopropanol; or a history of bronchial asthma, allergic disease, or serious concomitant disease, particularly renal impairment. Patients who were being considered for surgery; who were pregnant, lactating, or using inadequate contraceptive measures; or high-level (eg, professional) athletes wishing to resume normal training were also excluded. Patients were excluded if they had received treatment with any NSAID during the preceding week or if they were unlikely to comply with the study treatment and procedures.

The study was approved by the PMR Ethical Committee, Eastbourne, and was conducted in accordance with the current version of the Declaration of Helsinki (Hong Kong Revision, 1989). All patients gave written informed consent before entry.

At the initial visit (day 1), the nature, site, extent, and duration of the injury, and use of initial ICE therapy were noted. The extent of restriction of mobility, degree of stiffness, and global assessment of the injury's effect on the patient were assessed by the physician using a four-point rating scale (1 = none to 4 = severe). The patient also assessed the severity of the injury using a four-point rating scale (none to severe), and of pain at rest, on slight pressure, and on movement using a five-point rating scale (1 = no pain to 5 = intolerable pain).

Patients were then randomized consecutively to receive treatment with ketoprofen gel (2.5% w/w) 4 to 5 g three times daily (applied with or without a measuring device), piroxicam gel (0.5% w/w) 1 g three times daily, or diclofenac gel (1% w/w) 2 to 4 g three times daily, on a 2:2:1:1 basis. Patients were instructed to apply the gel by massaging it into the affected area, and to avoid covering the area with any occlusive dressing or protective bandage. The treatment period was 5 days. Treatment with paracetamol or coproxamol was permitted as rescue medication for symptomatic relief.

On day 5, assessments made at baseline were repeated. In addition, patients were asked to make the following assessments: acceptability of the treatment, in terms of ease of application, using a four-point scale (1 = very easy to 4 = very difficult), staining, cooling effect, and ease of rubbing in. Patients were also asked to make a global assessment of any change in the injury at the end of treatment, and determine the usefulness of the measuring device. The physician evaluated the overall response to treatment using a four-point scale (1 = none to 4 = excellent). Any observed or reported adverse events were noted.

Statistical Analysis

The study was analyzed on an intent-to-treat basis. The primary efficacy variable was the physician's assessment of the response to treatment at day 5. Initially, the two groups using ketoprofen gel (ie, with or without the measuring device) were compared for homogeneity with respect to each study variable using the Wilcoxon rank sum test. If the two groups did not differ significantly, data from each group were combined for analysis purposes. The Kruskal-Wallis one-way analysis of variance was used for between-group comparisons of the study efficacy variables and ease of application of the gel. If there was evidence of a significant difference between the treatments, individual treatment group comparisons were made using the Wilcoxon rank sum test. Chi-square tests were used for between-group comparisons of staining, cooling effect, and ease of rubbing in. The level of significance was $P = 0.025$ if the ketoprofen data were pooled, or $P = 0.0125$ if the data were not pooled (using a Bonferroni correction).[7]

RESULTS

A total of 1575 patients, 946 males and 624 females (sex was not specified for 5 patients) aged between 11 and 93 years (mean, 39 years), were recruited by 308 centers. A total of 1048 received ketoprofen gel (525 of whom used the gel in conjunction with the measuring device), 263 received piroxicam gel, and 264 received diclofenac gel. The treatment groups were comparable with respect to age and sex distribution (Table I) and the severity of the injury at baseline. Most patients had a moderate-to-severe injury, and almost all

Table I. Baseline characteristics.

Characteristic	Ketoprofen Gel (n = 1048) n = 523 Gel Alone n = 525 Gel + Applicator	Piroxicam Gel (n = 263)	Diclofenac Gel (n = 264)
Sex*			
Male	628	154	164
Female	416	109	99
Mean age in years (range)			
Male	36 (11–83)	34 (18–84)	35 (16–87)
Female	46 (13–93)	46 (18–83)	44 (14–78)
Initial ICE therapy (%)	13	13	15

ICE = ice/compression/elevation.
*Sex was not specified for four patients treated with ketoprofen gel and one patient treated with diclofenac gel.

patients had pain even at rest, with restriction in their mobility (Tables II and III).

Fifty-one patients (3%) failed to complete the study, primarily due to visit default (27 patients; Table IV). The majority of patients (88% to 90%) in each group complied with the treatment regimen, and returned for review between days 4 and 7. (Review was scheduled for days 4 and 5 unless day 5 was a Saturday or Sunday, in which case review was carried out on days 4, 6, or 7.)

Efficacy

With the exception of the data relating to restriction of mobility by the injury, there were no statistically significant differences between the two ketoprofen treatment groups for any variable (Wilcoxon rank sum test). Consequently, data from both groups were combined as a single treatment group for analysis purposes.

Treatment with ketoprofen gel was shown to be significantly more effective than with piroxicam gel (Table V). The physician global assessment of treatment response showed that improvement in the effect of injury was significantly better with ketoprofen gel than with piroxicam gel (74% vs 65%; $P = 0.0001$), and slightly better than with diclofenac gel (74% vs 71%). In addition, ketoprofen gel showed greater improvements in the degree of stiffness than piroxicam gel (71% vs 64%; $P = 0.013$), and in patient assessments of pain on pressure (81% vs 78%; $P = 0.02$) and pain on movement (83% vs 77%; $P = 0.01$). Nearly 50% of patients treated with ketoprofen gel showed a marked reduction (ie, great improvement) in pain on pressure as compared with less than 40% treated with either piroxicam gel or diclofenac gel; nearly 50% also reported a marked reduction in pain on movement with keto-

Table II. Patients' assessment of soft-tissue injury at baseline.

Characteristic	Ketoprofen Gel (n = 1048) n = 523 Gel Alone n = 525 Gel + Applicator	Piroxicam Gel (n = 263)	Diclofenac Gel (n = 264)
Pain at rest (%)			
None	9.3	9.5	9.8
Slight	40	37	41
Moderate	38	40	38
Severe	12	13	12
Intolerable	0.5	0	0
NR	0.4	0	0.4
Pain on pressure (%)			
None	0.5	0.8	0
Slight	10	11	13
Moderate	55	49	60
Severe	32	29	26
Intolerable	1.5	3.0	1.1
NR	0.5	0	0.4
Pain on movement (%)			
None	0.5	0.8	0.4
Slight	7.8	8.4	6.8
Moderate	54	53	57
Severe	35	34	33
Intolerable	2.4	3.4	1.5
NR	0.6	0	1.4
Global assessment of severity (%)			
None	0	0	0.4
Slight	11	12	11
Moderate	65	67	72
Severe	23	21	16
NR	0.2	0	0.4

NR = not recorded.
Rating scale: 1 = no pain to 5 = intolerable.
Severity scale: 1 = none to 4 = severe.

profen gel as compared with less than 40% with piroxicam gel (39.5%) and 44% with diclofenac gel. The patients' global assessment of improvement of the injury was also significantly higher with ketoprofen gel than with piroxicam gel: 38% of patients treated with ketoprofen as compared with 26% treated with piroxicam gel assessed their injury as greatly improved ($P = 0.0002$).

Table III. Physicians' assessment of soft-tissue injury at baseline.

Characteristic	Ketoprofen Gel (n = 1048) n = 523 Gel Alone n = 525 Gel + Applicator	Piroxicam Gel (n = 263)	Diclofenac Gel (n = 264)
Restriction of mobility (%)			
None	5.5	6.1	5.7
Slight	29	24	29
Moderate	56	59	60
Severe	8.7	10	4.9
NS	4.3	0	0.4
Stiffness (%)			
None	9.2	12	11
Slight	50	47	53
Moderate	34	35	33
Severe	6.4	5.7	2.7
NS	0.2	0	0.4
Global assessment of severity (%)			
None	0.2	0.8	0.4
Slight	23	23	25
Moderate	66	64	65
Severe	10	11	8.7
NS	0.4	0.4	0.8

NS = not stated.
Rating scale: 1 = none to 4 = severe.

Table IV. Reasons for withdrawal. Values represent number of patients.

	Ketoprofen Gel (n = 1048)			
	Gel Alone (n = 523)	Gel + Applicator (n = 525)	Piroxicam Gel (n = 263)	Diclofenac Gel (n = 264)
Failed to return	7	11	3	6
Deterioration of condition	2	1	0	2
Adverse event	2	0	2	0
Other	6	4	2	3
Total	17	16	7	11

Table V. Response to treatment. Values are given as number (%) of patients.

Assessment	Treatment			Statistical Significance*	
	Ketoprofen Gel (n = 1048)	Piroxicam Gel (n = 263)	Diclofenac Gel (n = 264)	Versus Piroxicam Gel	Versus Diclofenac Gel
Physician assessments					
Global assessments of treatment response†					
None	50 (5)	22 (8)	16 (6)		
Slight	172 (16)	61 (23)	47 (18)		
Improved	778 (74)	172 (65)	188 (71)	$P = 0.0001$	NS
Unassessable	48 (5)	8 (3)	13 (5)		
Improvement in stiffness	740 (71)	169 (64)	182 (69)	$P = 0.013$	NS
Improvement in effect of injury	712 (68)	178 (68)	180 (68)	NS	NS
Patient assessments					
Improvement in					
Pain at rest	789 (75)	192 (73)	192 (73)	NS	NS
On pressure	850 (81)	206 (78)	206 (78)	$P = 0.02$	NS
On movement	866 (83)	202 (77)	213 (81)	$P = 0.01$	NS
Global assessment of injury					
Slightly improved	439 (42)	134 (51)	130 (49)		NS
Greatly improved	396 (38)	69 (26)	80 (30)	$P = 0.0002$	

*Results of Wilcoxon rank sum test, ketoprofen versus comparator. Statistically significant if $P < 0.025$ (combined ketoprofen data).
†None = rating unchanged or deteriorated; slight or slightly = rating improved by 1 point; improved = rating improved by ≥2 points.

Physician-assessed improvement in mobility was significantly higher with ketoprofen gel (without the measuring device) as compared with piroxicam gel (34% vs 22%; $P = 0.006$), and it also compared favorably with diclofenac gel (34% vs 28%), although this difference did not reach statistical significance (data not shown).

Although about half of the patients (52%) found the device to be useful, provision of the measuring device appeared to offer little benefit. Any influence that the device may have had on compliance was insufficient to produce consistent superiority (either clinically or statistically) over the use of ketoprofen gel without the device.

Tolerability

All three treatments showed excellent tolerability. The incidence of drug-related adverse events was very low: 0.7% with ketoprofen gel, 1.1% with diclofenac gel, and 2.3% with piroxicam gel. Local skin reactions at the site of application (ie, erythema, rash, itching) were the most commonly reported drug-related adverse events. Four patients (two each treated with ketoprofen gel and piroxicam gel) were withdrawn due to suspected adverse reactions. In the ketoprofen groups, one patient reported nausea and anorexia, and one patient reported increased ankle swelling. In the piroxicam group, one patient reported headache and a general feeling of malaise, and one patient developed a urticarial rash. All events subsequently resolved without the need for further intervention.

Acceptability

Patients preferred treatment with ketoprofen gel (Table VI). It was significantly easier to rub in than piroxicam gel (89% vs 81%), was rated by more patients as having a cooling effect than either competitor (71% vs 49% for piroxicam gel; 71% and 60% in comparison with diclofenac gel), and produced markedly less staining than piroxicam gel (4% vs 31%).

DISCUSSION

As mentioned previously, the efficacy of ketoprofen gel has been documented in placebo-controlled studies.[4–6] The aim of this study was to compare the efficacy, tolerability, and acceptability of ketoprofen gel with other well-established therapies. An open-label study design was adopted as it was not practical to use double-dummy techniques. However, despite the lack of placebo control, this study of 1575 patients provides meaningful and interesting comparative data on the three gels studied.

This study confirms the efficacy, tolerability, and acceptability of ketoprofen gel in the treatment of acute soft-tissue injury in general practice. Not only was ketoprofen gel significantly more effective than piroxicam gel in alleviating stiffness and pain associated with the injury, it improved mobility as well. Global assessments made by both the physician and patient, often a more accurate measure of treatment response in clinical studies,[8] significantly favored the use of ketoprofen gel.

Differences between ketoprofen gel and diclofenac gel were less marked and not statistically significant. However, for almost all efficacy variables, a larger proportion of patients treated with ketoprofen gel showed great improvement (ie, "greatly improved") as compared with those treated with diclofenac gel. Thus there is evidence to suggest that the use of

Table VI. Patients' assessment of the acceptability of treatment. Values are given as percentage of patients.

	Treatment			Statistical Significance*	
Assessment	Ketoprofen Gel (n = 1048)	Piroxicam Gel (n = 263)	Diclofenac Gel (n = 264)	Versus Piroxicam Gel	Versus Diclofenac Gel
Easy/very easy to apply	95	97	94	$P = 0.002$	NS
Easy to rub in	89	81	87	$P < 0.001$	NS
Cooling effect	71	49	60	$P < 0.001$	$P = 0.001$
Staining	4	31	4	$P < 0.001$	NS

*Results of Wilcoxon rank sum test, ketoprofen gel versus comparator. Statistically significant if $P < 0.025$ (combined ketoprofen data).

ketoprofen gel may offer some additional benefit over diclofenac gel.

Ketoprofen gel showed significantly better patient acceptability than piroxicam gel in terms of ease rubbing in, and there was far less staining. Moreover, more patients noted a marked cooling effect with ketoprofen gel, which was significantly greater than that noted with either piroxicam or diclofenac gels. Provision of a measuring device as an aid to application and compliance offered little additional benefit to the use of the ketoprofen gel.

The tolerability of ketoprofen gel was excellent. The very low incidence of drug-related adverse events with ketoprofen (0.7%) compared favorably with that reported for piroxicam (2.3%) and diclofenac (1.1%) gels, and was consistent with that previously reported in a very large, general practice study involving more than 18,000 patients and 3000 general practitioners (1.17%).[9]

CONCLUSION

The efficacy and patient acceptability of ketoprofen gel in the treatment of acute soft-tissue injury were superior to those of piroxicam gel. In addition, ketoprofen gel may offer some additional benefit over the use of diclofenac gel in terms of patient acceptability. Ketoprofen gel would be a useful addition to the range of established treatments for acute soft-tissue injury in general practice.

ACKNOWLEDGMENTS

This study was funded by Clinical Research, Rhône-Poulenc Rorer (UK) Ltd., Eastbourne, East Sussex, United Kingdom. The authors would also like to thank the members of the General Practice Study Group for their participation.

Address correspondence to: P.F. Leswell, CBiol, MIBiol, Clinical Research Coordinator, Rhône-Poulenc Rorer (UK) Ltd., RPR House, 52 St Leonards Road, Eastbourne, East Sussex, BN21 3YG, United Kingdom.

REFERENCES

1. *Everyday Healthcare—A Consumer Study of Self Medication in Great Britain.* London: The British Market Research Bureau; 1987.

2. Veys EM, ed. 20 years experience with ketoprofen. *Scand J Rheumatol.* 1991;20 (Suppl 90):3–44.

3. Le Liboux A, et al. Rapport d'expertise sur l'absorption cutanée de trois préparations topique de kétoprofène. Rhône-Poulenc, Paris, France, internal report.

4. Ballerini R, Casini A, Chinol M, et al. Study on the absorption of ketoprofen topically administered in man: Comparison between tissue and plasma levels. *Int J Clin Pharmacol Res.* 1986;VI:69–72.

5. Kockelbergh M, Verspeelt P, Caloine R, et al. Local anti-inflammatory treatment with a ketoprofen gel: Recent clinical data. *Medica Physica.* 1985;8:205–213. In French.

6. Noret A, Roty V, Allington N, et al. Ketoprofen gel as topical treatment for sport injuries. *Acta Ther.* 1987;13:367–378.

7. Miller RG. *Simultaneous Statistical Inference.* New York: Springer-Verlag; 1981: 67–70.

8. Huskisson EC. Clinical trials and therapeutic evaluation. In: Scott JT, ed. *Copeman's Textbook of the Rheumatic Disease.* 6th ed. Vol. 2. Edinburgh: Churchill Livingstone; 1986:1581–1596.

9. Portes G, Raynaud O. Profenid gel national study. 88% Satisfaction. *La Gazette Medicale.* 1990;97(Suppl):1–4.