Rheumatology 1999;38:564–567

Intra-articular absorption and distribution of ketoprofen after topical plaster application and oral intake in 100 patients undergoing knee arthroscopy

C. Rolf, B. Engström, C. Beauchard[1], L. D. Jacobs[1] and A. Le Liboux[1]

Section of Sports Medicine, Department of Orthopaedic Surgery, Huddinge University Hospital, S-14186 Huddinge, Sweden and [1]Rhône-Poulenc Rorer, 92165 Antony, France

Abstract

Objective. The primary objective of this study was to assess the kinetics of ketoprofen in synovial fluid and intra-articular tissues in relation to plasma. The secondary objective was to study whether intra-articular tissues act as reservoirs.

Methods. The ketoprofen concentration was analysed in plasma, synovial fluid and intra-articular tissues after single application of a 30 mg plaster ($n = 40$), multiple applications for 5 days ($n = 30$) or oral intake of 50 mg ($n = 30$) in patients undergoing knee arthroscopy.

Results. Median CMax values after topical application were 12.8 ng/ml in synovial fluid, 56.7 ng/g in synovial tissue, 349.3 ng/g in meniscus and 568.9 ng/g in cartilage.

Conclusion. Topical applications of ketoprofen allow the attainment of high intra-articular tissue concentrations.

KEY WORDS: Knee joint, Absorption, Ketoprofen, Synovial tissue.

There has been a growing interest in percutaneous administration of anti-inflammatory drugs for the treatment of local conditions, one main feature being a reduction in systemic exposure compared with oral administration. Ketoprofen [2-(3-benzoyl phenyl) propionic acid] is a non-steroidal anti-inflammatory agent used in a variety of rheumatic and musculoskeletal conditions [1]. Ballerini *et al.* [2] showed high levels of ketoprofen in intra-articular adipose tissue and in capsular tissue after gel application. Low plasma and synovial fluid levels were found after ketoprofen gel applications ($n = 12$), compared with oral administration ($n = 12$), but a comparable tissue penetration, as assessed by similar concentrations in intra-articular tissues [3]. In another arm of the same study, we observed that topical ketoprofen penetrated the skin into soft tissues and also into the Achilles tendon [4].

The primary objective of this study was to assess intra-articular absorption and distribution of ketoprofen after topical plaster application in relation to plasma level. The secondary objective was to attempt to verify that tissues may act as reservoir of ketoprofen, by evaluating tissue concentrations at various time points after removal of the plaster, related to plasma.

Submitted 10 March 1998; revised version accepted 10 February 1999.

Correspondence to: C. Rolf, Section of Sports Medicine, Department of Orthopaedic Surgery, Huddinge University Hospital, S-14186 Huddinge, Sweden.

Materials and methods

Patients to be included were of both sexes, aged 18–65 yr, suffering from knee disorders requiring arthroscopy. Exclusion criteria were a history of gastric or duodenal ulcer, known hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs), bronchial asthma or allergic disease, pregnancy, open wounds or skin pathology, serious concomitant renal, cardiac, hepatic or other disease. The minimum wash-out period prior to study treatment administration was 3 weeks for ketoprofen, 1 week for any other form of NSAID or steroids, and 24 h for aspirin. The study was approved by the local ethics committee at Huddinge University Hospital Karolinska Institutet, Stockholm, Sweden, and monitored in accordance with good clinical practices and Rhône-Poulenc Rorer monitoring procedures. Before commencing the study, each patient gave their informed consent to participate and to adhere to the procedures described in the protocol.

Ketoprofen was administered either topically (T; 30 mg plasters worn for 24 h) in single application (SA; 40 patients) or multiple application for five consecutive

days (MA; 30 patients), or orally (single intake of one ketoprofen 50 mg immediate-release capsule: O; 30 patients). The interval between two applications of plasters was supported by an earlier pharmacokinetic study showing a plateau concentration of ketoprofen in plasma until the 24th hour of application [5]. The choice of oral dose was not based on an equipotency hypothesis of the topical and oral doses regarding pain relief, but rather on the fact that 50 mg is a commonly used single oral dose. Obviously, only one surgical sampling per patient was possible. Surgery was performed at given times (randomly allocated) to explore various features of ketoprofen kinetics: absorption and distribution after single topical (1, 2, 6 and 14 h after application) and oral administration (2, 6 and 14 h after intake), concentrations at steady state and elimination after multiple topical administration (0, 6 and 14 h after removal of the last of five plasters). As substantiated below, 10 subjects per sampling time were studied. Blinding of the administration was not deemed necessary due to the purely kinetic objective of the study. However, the laboratory which performed the assays did not know the treatment allocation.

Blood samples were taken from an antecubital vein at baseline, and concomitant with the anterolateral skin incision during arthroscopy. Biopsies were taken consecutively: synovial fluid from a lateral position, from synovial tissue under endoscopic visualization, and from cartilage and meniscus when appropriate (loose bodies, arthritis and partial meniscal tears). Samples were immediately deep frozen.

The analyses of plasma, synovial fluid and tissue samples were performed with a gas chromatography/mass spectrometry (GC/MS assay) method after derivatization (alkylation of the carboxyl group) of ketoprofen. The linearity of this method was verified from 0.5 to 100 ng/ml in plasma and from 0.5 to 100 ng/50 mg in each tissue (synovial tissue–cartilage–meniscus) [6]. The limit of quantification was validated at 0.5 ng/ml for plasma and 0.5 ng/50 mg for tissues. Tissue concentrations in nanograms per gram were calculated by using weights automatically transferred to an EXCEL program via a serial interface. The pharmacokinetic analyses of experimental data were performed at the Department of Drug Metabolism and Pharmacokinetics, Rhône-Poulenc Rorer, Antony, France.

Owing to high interindividual variability mainly related to the high variability of the weight of collected samples, median, minimum and maximum individual levels and number of observations were used. The median maximum concentration (CMax) was the highest value observed after administration (single application) or after removal of the plaster (multiple applications), and used for comparison between oral intake and topical administration. On the assumption of a mean concentration of 0.25 ng/ml of ketoprofen in synovial fluid and tissues with a S.D. of 0.16, 10 subjects per sampling time would give a precision of 0.10 for the measure, i.e. a mean confidence interval length of <0.20. Plasma and synovial fluid levels were also expressed as the median for comparison with tissue concentration. No further statistical analysis was performed.

Results

The mean duration of symptoms prior to surgery was 17 months (range 10–26 months). The mean age was 37.9 yr for the single-topical-application group (five females, 35 males), 35.8 yr for the multiple-application group (seven females and 23 males) and 37 yr for the oral intake group (nine females, 21 males). Weight, stature and duration of symptoms prior to arthroscopy did not differ between the groups. Three patients in the multiple-application group were either lost to follow-up ($n = 1$) or withdrew their consent during the study ($n = 2$).

Synovial fluid was taken from 80% ($n = 32/40$) of the SA group, 70% ($n = 20/28$) of the MA patients and 56.7% ($n = 17/30$) of the O group. Synovial tissue was taken from 98% ($n = 96/98$), cartilage from 23% ($n = 23/98$) and menisci from 52% ($n = 51/98$) of the patients, similar within each group. The specimens varied inter-individually in weight, synovial tissue (0.60–83.70 mg), cartilage (0–55.26 mg) and meniscus (0.43–64.77 mg).

Median concentrations at various sampling times, numbers of samples with concentrations above the quantification limit and number of samples available are presented in Table 1. The main reason for concentrations below the quantification limit was the small weight of the sample.

After topical administration, ketoprofen penetrates through the skin into the plasma, reaching a steady state at 14 h which is maintained after repeated administration (18.1 ng/ml at 14 h after SA, 18.7 ng/ml at removal of the last of five plasters in MA). Ketoprofen penetrates through the skin into the synovial fluid, although the steady state seems to be reached later than in plasma (8.9 ng/ml at 14 h after SA, 12.8 ng/ml at removal of the last of five plasters in MA); however, ketoprofen penetrates into the synovial tissue apparently slower than in surrounding structures [below limit of quantification (BLQ) at 14 h after SA, 56.7 ng/g at removal of the last of five plasters in MA]. Ketoprofen penetrates into meniscus (349.3 ng/g at 14 h after SA) and in cartilage (569 ng/g at removal of the last of five plasters in MA).

After oral application, concentrations in the plasma and synovial fluid follow the known features for ketoprofen, with a delayed curve in the synovial fluid; ketoprofen also penetrates into intra-articular tissues, the highest concentration being seen in synovial tissue.

Median CMax concentrations in fluids and intra-articular tissues are presented in Table 2. Topical administration/oral intake ratios were 0.2 for synovial tissue, 4.1 for meniscus and 6.8 for cartilage.

Discussion

The two types of administration of ketoprofen evaluated in this study are fundamentally different. The kinetics

TABLE 1. Median concentrations of ketoprofen in plasma, synovial fluid and knee joint tissues (and mean synovial fluid/plasma ratios) after single (SA) or multiple (MA) topical or single oral (O) administration

Treatment	Time (h)	Plasma (ng/ml)[a]	Synovial fluid (ng/ml)[a]	Ratio synovial fluid/ plasma[b]	Synovial tissue (ng/g)[a]	Meniscus (ng/g)[a]	Cartilage (ng/g)[a]
SA	1	BLQ	0.4	–	BLQ	16.1	BLQ
after application		0/10	6/8		1/10	3/5	0/4
	2	2.9	1.0	0.66 (± 0.70)	BLQ	32.6	BLQ
		9/10	5/7	5	3/10	2/4	1/4
	6	21.5	6.8	0.37 (± 0.12)	BLQ	22	BLQ
		10/10	7/7	7	3/10	5/8	0/1
	14	18.1	8.9	0.68 (± 0.54)	BLQ	349.3	BLQ
		10/10	10/10	10	4/10	6/7	0/1
MA	0	18.7	12.8	0.70 (± 0.25)	56.7	BLQ	569
after removal		10/10	6/6	6	7/10	1/4	2/2
of last plaster	6	8.8	6.3	0.77 (± 014)	29.4	10.6	11.1
		9/9	8/8	8	5/8	2/5	2/3
	14	4.8	5.7	0.81 (± 0.22)	BLQ	(399.3)	–
		8/8	5/5	5	3/7	1/1	
O	2	2595.3	350.7	0.16 (± 0.08)	363.9	25.6	83.5
after intake		10/10	5/5	5	7/10	4/7	1/2
	6	483.3	353.8	0.83 (± 0.36)	212.6	85.7	54.2
		10/10	7/7	7	7/10	3/4	3/4
	14	47.2	37.9	1.09 (± 0.81)	BLQ	17.4	BLQ
		10/10	5/5	5	2/10	3/5	0/2

BLQ, below the limit of quantification.
[a]Median concentration; number of samples above quantification limit/number of samples available.
[b]Mean (± S.D.) number of patients for whom both values were above the quantification limit.

of ketoprofen after oral administration of immediate-release forms are well known: absorption is complete and concentrations are proportional to the dose administered in the range of doses used in clinical practice, both in plasma and synovial fluid. The plaster is a slow continuous-release form, where ketoprofen has to penetrate through the skin. Previous data indicate that the absorption of ketoprofen through the skin is no longer likely to be proportional to the dose applied, as soon as this dose exceeds a small amount. The patch contains a large excess of active substance as compared to the absorption capacities of the skin, as demonstrated in a study based on urine excretion [3], where only ~6 mg of ketoprofen were absorbed through the skin during the 24 h during which the 30 mg plaster was worn, Therefore, no measurement of doses actually absorbed was performed in this study, and no direct dose-adjusted comparison was made; however, it is worthwhile mentioning that, based on the above-mentioned study, 2 h after application of the plaster, at most 1 mg would have been absorbed, to be compared to 50 mg after oral administration.

This study shows that a direct penetration of ketoprofen through the skin is most likely: 1 h after SA, some substance was measured in the synovial fluid in 6/8 subjects, whereas no sample of plasma showed any measurable concentration; moreover, the median CMax ratios T/O for meniscus and cartilage (Table 2), as well as the T/O ratio at 2 h after SA *vs* O (32.6/25.6 = 1.27), clearly reinforce the hypothesis, mostly when considering the disparity of absorbed doses described above. After topical application, steady state was achieved later in the synovial fluid than in plasma. However, once this state was reached, plasma and synovial fluid levels appeared comparable, as shown in the decline after removal of the last plaster. The less impressive T/O ratio observed for synovial tissue is likely to be due to the fact that, contrary to meniscus and cartilage, this tissue is highly vascularized, and therefore receives ketoprofen both directly and through the general circulation, as known from previous studies. Similarly, due to the mechanism of formation of synovial fluid (mostly from the plasma), levels of drug in synovial fluid are not good estimates of tissue penetration. The clearance rate of knee joint synovial fluid components has been shown to vary in different joint diseases [7]. With the limitation of few collected samples, our results indicate that intra-articular tissues, such as cartilage and menisci, may act as reservoirs for ketoprofen.

TABLE 2. Median CMax (ng/g tissue, ng/ml fluid) of ketoprofen after topical application (T = single or multiple application) and oral intake (O) in 100 subjects undergoing knee arthroscopy

Tissue	Median CMax T	Median CMax O	T/O ratio
Synovial tissue	56.7	363.9	0.2
Meniscus	349.3	85.7	4.1
Cartilage	568.9	83.5	6.8
Plasma	18.7	2595.3	0.0034
Synovial fluid	12.8	353.8	0.036

This study confirms that topical applications of ketoprofen allow the attainment of high intra-articular concentrations, whereas plasma levels and systemic exposure are low. The high concentrations reached in cartilage raise the highly debated question of the deleterious effect

of NSAIDs on cartilage, which would deserve further investigations. Even if a reservoir effect exists, it would be of short duration due to the short half-life of ketoprofen; moreover, topical treatments are unlikely to be long term, and several *in vitro* studies indicate that ketoprofen has no deleterious effect on cartilage [8–11]. Similar results regarding synovial fluid/plasma ratios have been obtained after the administration of other topical NSAIDs [12, 13], although there are conflicting reports on the depth and quantity of NSAIDs delivered to local s.c. structures after topical application [14]. Our data support the rationale for further analyses of therapeutic effects [15–22], which should obviously be in double-blind conditions, using designs which overcome the usually significant improvement observed with topical 'placebo' formulations, probably at least partly due to the beneficial effect of excipients (menthol, etc.) and/or of massage or bandage.

In conclusion, our results indicate that applications of ketoprofen plasters allow the attainment of high intra-articular concentrations, with limited systemic exposure, and that less vascularized tissues may act as reservoirs.

References

1. Veys EM. 20 years' experience with ketoprofen. Scand J Rheumatol 1991;20(suppl. 90):3–44.
2. Ballerini R, Casini A, Chinoi M, Manuchi C, Giaccai L, Salvi M. 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.
3. Le Liboux A, Gautier J, Montay G. A study to assess the absorption into knee joint of ketoprofen after oral and topical application. Internal Report, Rhône-Poulenc Rorer, 1995.
4. Rolf C *et al*. An open, randomized study of ketoprofen in patients in surgery for Achilles or patellar tendinopathy. J Rheumatol 1997;24:1595–8.
5. LeLiboux A, Borg M, Lefebvre P, Montay G, Frydman A. RP 19583 (Ketoprofen)—A phase I open tolerability and pharmacokinetic study of ketoprofen administered as a plaster (30 mg) for 15 days in 16 healthy male volunteers. Internal Report, Rhône-Poulenc Rorer, 1992.
6. Gautier J, Le Liboux A, Montay G. GC/MS determination of ketoprofen in synovial fluid, plasma and target tissues (skin, Achilles tendon, paratendon, fatty tissue). In: 5th International Symposium on Pharmaceutical and Biomedical Analysis, Stockholm, Sweden, September 21–23, 1994.
7. Wallis W, Simkin P, Nelb W. Protein traffic in human synovial effusions. Arthritis Rheum 1987;30:57–63.
8. Collier S *et al*. Comparison of the effects of non-steroidal anti-inflammatory drugs (NSAIDs) on proteoglycan synthesis by articular cartilage explant and chondrocyte monolayer cultures. Biochem Pharmacol 1991;41:1375–84.
9. Wilbrink B *et al*. *In vitro* influence of ketoprofen on the proteoglycan metabolism of human normal and osteoarthritis cartilage. Agents Actions 1991;32:154–9.
10. Huber-Bruning O *et al*. Potential influences of ketoprofen on human healthy and osteoarthritic cartilage *in vitro*. Scand J Rheumatol 1989;83(suppl.):29–32.
11. Kalbhen DA. The influence of NSAIDs on morphology of articular cartilage. Scand J Rheumatol 1988; 77(suppl.):13–22.
12. Rademacher J, Jeutsch D, Scholl M, Lustinetz T, Fröhlich J. Diclofenac concentrations in synovial fluid and plasma after cutaneous application in inflammatory and degenerative joint disease. Br J Clin Pharmacol 1991;31:537–41.
13. Bannwarth B, LeHuec J, Vincon G, Labat L, Demotes-Mainard F, Rivalle F. Tissue and systemic diffusion of idrocilamide after cutaneous administration. Rev Rhum Ed Fr 1993;60:932–6.
14. Singh P, Roberts M. Skin permeability and local tissue concentrations of non steroidal anti inflammatory drugs after topical application. J Pharmacol Exp Ther 1994;268:144–51.
15. Muckle D. Comparative study of ibuprofen and aspirin in soft tissue injuries. Rheumatol Rehabil 1974;13:141–7.
16. Santilli G, Tuccimei U, Cannistra F. Comparative study with piroxicam and ibuprofen versus placebo in the supportive treatment of minor sports injuries. J Int Med Res 1980;8:265–9.
17. McLatchie G, Allister C, MacEwen C. Variable schedules of ibuprofen for ankle sprains. Br J Sports Med 1985;19:203–6.
18. Huskisson E, Berry H, Street F, Medhurst H. Indomethacin for soft tissue injuries. A double blind study in football players. Rheumatol Rehabil 1973;12:159–60.
19. Andersson S, Fredin H, Lindberg H, Sanzen L, Westlin N. Ibuprofen and compression bandage in the treatment of ankle sprains. Acta Orthop Scand 1983;54:322–5.
20. Duranceau J, Lacoste P. Double blind comparison of ketoprofen and placebo in the treatment of sprains and strains. Clin Ther 1986;8:187–95.
21. Dupont M, Beliveau P, Theriault G. The efficacy of antiinflammatory medication in the treatment of the acutely sprained ankle. Am J Sports Med 1987;15:41–5.
22. Åström M, Westlin N. No effect of piroxicam on Achilles tendinopathy. A randomized study of 70 patients. Acta Orthop Scand 1992;63:631–4.