

Topical NSAIDs: plasma and tissue concentrations

Clinical bottom line

Topical NSAID administration results in peak plasma concentrations that are much lower than after oral administration of standard NSAID doses. Plasma concentrations after topical administration are generally less than 5% of those in plasma.

Synovial fluid concentrations are also lower, but concentrations in meniscus or cartilage are 4-7 times higher than after oral administration.

Concentrations in tendon sheath are several hundred times greater than plasma concentrations after topical administration

Plasma

Ibuprofen

Plasma concentrations after topical administration are generally low. Studies that have measured plasma concentrations, after single or multiple applications, generally find concentrations to be below about 500 ng/mL (Table 1). The exception was one study in six volunteers with a single application of one of three ibuprofen preparations, in which the mean plasma concentration was about 1,400 ng/mL. For the two other preparations the maximum plasma concentrations were much lower, less than 400 ng/mL.

These concentrations are very much lower than peak concentrations with oral ibuprofen at usual doses of about 400 mg, where peak concentrations are generally above 20,000 ng/mL (20 µg/mL).

Table 1: Plasma and tissue concentrations after topical NSAID application

Reference	Design	Results
Plasma and tissue concentrations		
Cagnie et al. Physical Therapy 2003 83 6: 707-712	26 patients undergoing knee arthroscopy used 2.5% ketoprofen cream with and without ultrasound for 5 minutes 47-77 minutes before arthroscopy. Synovial tissue and a blood sample 2 hours after topical administration were collected	Plasma levels below 4 ng/mL in most patients Synovial tissue 2 µg/g without ultrasound, but about 20-30 µg/g with ultrasound, with wide variation
Osterwalder et al. Arzneimittel-Forsch 2002 52: 822-827	10 patients undergoing knee arthroscopy or carpal tunnel release treated with ketoprofen patch 6 days before surgery. Tissue and blood samples were collected	Plasma concentration 13-112 ng/mL Synovial tissue 20-430 ng/g Tendon sheath 13-32 µg/g
Tegeder et al. Pharm Res 2001 18: 980-986	8 volunteers given single dose 100 mg ketoprofen topically. Tissue dialysis and blood samples taken	Plasma levels 10-50 ng/mL by 8 hours Muscle and subcutaneous tissue below 20 ng/mL
Tedeger et al. Clin Pharmacol Ther 1999 65: 357-368	11 volunteers given single dose 800 mg oral ibuprofen or 16 g 5% ibuprofen gel. Tissue dialysis and blood samples taken	Higher subcutaneous tissue dialysate concentrations and similar muscle dialysate concentrations with topical compared with oral
Rolf et al. Rheumatology 1999 38: 564-567	100 patients with knee disorders requiring arthroscopy. Single application topical ketoprofen in 40, multiple applications for 5 days in	Higher concentrations in plasma, synovial fluid and synovial tissue after oral than topical, but higher levels in meniscus and cartilage for topical than oral

	30, or single dose 50 mg oral ketoprofen	administration
Dominkus et al. <i>Arzneim-Forsch</i> 1996 46: 1138-1142	17 patients with degenerative knee disorders given 1200 mg oral ibuprofen daily or topical ibuprofen daily for 3 days. Blood and synovial fluid samples taken	Topical administration produced higher concentrations in fasciae, muscle and subcutaneous tissue than in plasma. Concentrations of ibuprofen were in therapeutically effective levels 15 hours after topical or oral administration
Gallacchi & Marcolongo. <i>Drugs Exptl Clin Res</i> 1993 XIX: 97-100	8 patients with knee joint effusion used diclofenac plasters for 4 days. Blood samples and synovial fluid samples collected	After four days max plasma concentration of diclofenac was 3.6 ng/mL, and synovial fluid concentration 1 ng/mL
Radermacher et al. <i>Br J Clin Pharmacol</i> 1991 31: 537-541	10 patients with bilateral knee effusion treated with diclofenac gel for 3 days. Randomised double-blind to active or control on different knees. Blood and synovial fluid samples collected.	Plasma concentration of diclofenac about 40 ng/mL Synovial fluid 26 ng/mL in treated and 22 ng/mL in untreated knee
Berner et al. <i>Drugs Exptl Clin Res</i> 1989 XV: 559-564	10 volunteers and 8 patients with OA knee had either a single application ibuprofen or 3 times daily ibuprofen for 3 days. Blood and tissue samples collected as appropriate.	In volunteers, plasma ibuprofen was 100-200 ng/mL Patients had end of study blood concentration of 90 ng/mL Tissue concentrations were 7 µg/g in capsule, 9 µg/g in tendon and 20 µg/g in muscle
Ballerini et al. <i>Int J Clin Pharm Res</i> 1986 VI: 69-72	6 patients had ketoprofen gel applied daily for 3 days before operation, with 12 hours before operation. Blood, synovial fluid, and capsule samples taken	Plasma concentrations of ketoprofen about 18 ng/mL Synovial fluid 1,300 ng/mL Capsule 2.4 µg/g

Plasma concentrations

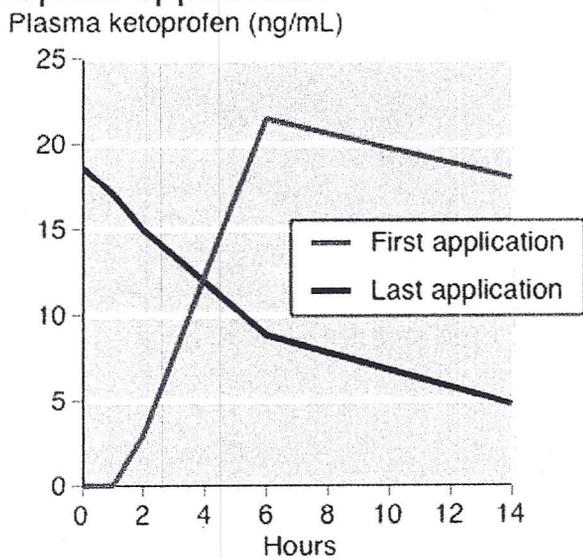
Cannavino et al.	32 men performing exercise	Significant reduction in
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Clin J Sports Med 2003 13: 200-208	to produce delayed action muscle soreness. Randomly assigned to topical ketoprofen or placebo to either or both legs. Pain scores and plasma concentrations	muscle soreness with ketoprofen. Plasma concentrations in range of 23-53 ng/mL
Steen et al. Europ J Pain 2000 4: 195-209	19 volunteers in two studies of experimental cutaneous or muscle pain treated with topical or oral ibuprofen in randomised, double blind studies. Pain scores and plasma concentrations	Pain effectively treated with ibuprofen with both routes. After 800 mg oral ibuprofen, plasma concentrations were 13-25 µg/mL 30-90 minutes after dose. With application of 5% topical ibuprofen gel plasma concentrations were 43-62 ng/mL 45-90 minutes after dose.
Seth. Arzneim- Forsch 1993 43: 919-921	6 volunteers randomised to cross over with single application of ibuprofen preparations one week apart. Blood samples taken	Mean maximum plasma concentrations were: gel 1,400 ng/mL ointment 280 ng/mL cream 390 ng/mL
Seth. Arzneim- Forsch 1992 42: 120-122	7 volunteers randomised to cross over with single application of diclofenac preparations one week apart, and IM diclofenac 25 mg. Blood samples taken	Mean maximum plasma concentrations were: emulsion 1: 81 ng/mL emulsion 2: 39 ng/mL IM: 900 ng/mL
van den Ouweland et al. Eur J Clin Pharmacol 1989 36: 209-211	15 volunteers given single application of 10% and 5% naproxen gel. Blood samples taken	Maximum plasma concentrations were: 10% gel 40 ng/mL at 24 hours 5% gel 42 ng/mL at 48 hours
Flouvat et al. Arzneim-Forsch 1989 39: 812-815	10 volunteers used topical ketoprofen twice a day for 10 days. Blood samples taken.	Mean plasma concentrations were about 150-200 ng/mL after 10 days, and peak was 144 ng/mL after first administration

Ketoprofen

For ketoprofen, plasma concentrations after a single application were generally below 50 ng/mL and after multiple applications were about 150-200 ng/mL (Table 1). A detailed study of single and multiple applications of ketoprofen in a large number of patients [1], mean plasma concentrations were no higher than about 20 ng/mL (Figure 1). These levels were achieved within six hours of the first application, but fell away rapidly after the last application was removed, following five days of multiple applications.

Figure 1: Plasma kinetics of ketoprofen after first and last doses of topical application



After oral ketoprofen, peak plasma concentrations were at least two orders of magnitude higher, at 2,600 ng/mL two hours after a single 50 mg dose, and were at least twice as high as the maximum value after topical application even 14 hours after an oral dose (Figure 2).

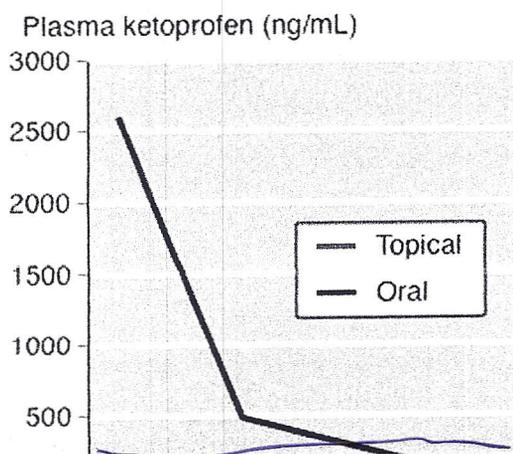


Figure 2: Plasma concentrations of ketoprofen after topical and oral application

Diclofenac

Topical diclofenac produced maximum concentrations in plasma of 4-80 ng/mL

after single or multiple applications (Table 1).

Synovial fluid

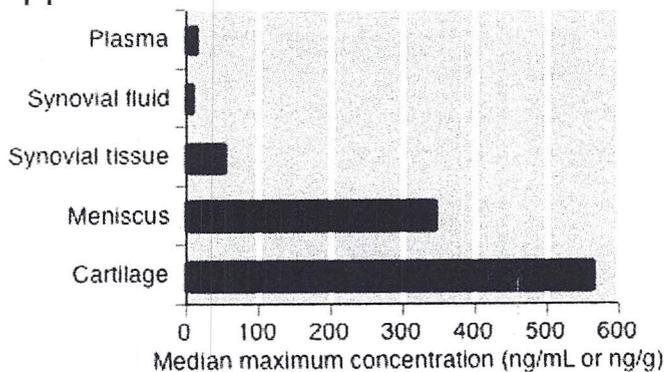
Synovial fluid concentrations of NSAIDs after topical application were generally lower than those found in plasma. The largest study [1] of ketoprofen found that the ratio of synovial fluid to plasma concentration was of the order of 0.6 to 0.8 at most times after the first or last dose.

Other tissues

Concentrations of NSAID in tissue after topical administration tended to be higher. For instance, after three days of application of topical ketoprofen, concentrations in the knee capsule were 2.4 $\mu\text{g/g}$, and after three days of topical ibuprofen were 7-9 $\mu\text{g/g}$ in capsule and tendon. After a single dose, other studies found concentrations about a thousand-fold higher than plasma concentrations in subcutaneous tissue, muscle, and tendon sheath.

In the largest single study [1], very high concentrations of ketoprofen were found in meniscus and cartilage after topical administration, about 4-7 times greater than were found after oral administration, despite lower plasma concentrations (Figure 3).

Figure 3: Tissue concentrations of ketoprofen after topical application



Comment

This brief review confirms the view of others [2], that the maximum values found after topical administration of NSAIDs is a small fraction of that expected after usual oral doses of the same NSAID. These low systemic concentrations probably account for the low occurrence of gastrointestinal adverse events with topical NSAIDs.

As best we can tell, synovial fluid concentrations are likely to reflect blood concentrations because this is a highly vascularised compartment. For instance, when topical diclofenac was applied to one knee in a randomised and double blind trial [3], the concentration of diclofenac in the untreated knee was almost the same as that in the treated knee.

However, concentrations of NSAID in tissue, particularly meniscus and cartilage, were very much higher after topical than oral administration, indicating that direct absorption through the skin into tissues of the joint does occur.

References

1. C Rolf et al. Intra-articular absorption and distribution of ketoprofen after topical plaster application and oral intake in 100 patients undergoing knee arthroscopy. *Rheumatology* 1999 38: 564-567.
2. CA Heyneman et al. Oral versus topical NSAIDs in rheumatic diseases. A comparison. *Drugs* 2000 60: 555-574.
3. J Radermacher et al. Diclofenac concentrations in synovial fluid and plasma after cutaneous application in inflammatory and degenerative joint disease. *British Journal of Clinical Pharmacology* 1991 31: 537-541.