

Analgesic Efficacy and Pharmacokinetics of Ketoprofen Administered into a Surgical Site

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A series of three clinical trials in the oral surgery model evaluated the analgesic efficacy and pharmacokinetics of ketoprofen administered locally as a strategy for decreasing systemic exposure to nonsteroidal anti-inflammatory drugs (NSAIDs). A gel formulation was administered directly into extraction sites 1 hour following oral surgery, and pain intensity was evaluated for 6 hours. Significantly less pain was seen following peripheral administration of both 10 and 30 mg ketoprofen in comparison to the placebo. In a second study, peripheral administration of the 10 mg dose resulted in greater analgesia

than oral administration of the same dose formulation or the placebo. The third study demonstrated lower plasma drug levels following the peripheral route of administration in comparison to oral administration of the same dose or ingestion of a 25 mg oral capsule. These data indicate that administration of an NSAID to a peripheral site of tissue injury results in greater analgesia than oral administration and suggests the potential for less drug toxicity through lower circulating drug levels.

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INTRODUCTION

The efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) for acute and chronic pain is well recognized but is often accompanied by undesirable effects secondary to systemic distribution. Epidemiologic studies, for example, demonstrate that NSAIDs increase the risk of ulcerations and perforation in the small intestine in long-term NSAID users and result in more frequent ulcerations even in short-term users of this drug class.¹ The relative risk of upper GI bleeding is increased fivefold by ingestion of NSAIDs,² is elevated in the elderly,³ and may be even higher for certain NSAIDs.^{4,5} Alterations in renal function associated with NSAID ingestion are estimated to occur in approximately 1% of exposed patients⁶ and may include a wide array of untoward renal effects

resulting in significant abnormalities.⁷ The risk of end stage renal disease requiring dialysis is attributed to a high cumulative ingestion of NSAIDs,⁸ with recognition that nonprescription use of NSAIDs, particularly in combination with other similar drugs, represents a potential renal risk.⁹

One approach to overcoming these therapeutic limitations is to maximize drug levels at the site of action and minimize systemic exposure by administering the drug directly to the site of tissue injury. Local application of aspirin and acetaminophen at subtherapeutic doses (50 mg) has been demonstrated to produce analgesia in comparison to the placebo and systemic administration of the same dose.¹⁰ An aspirin solution applied topically in the oral cavity produces an analgesic effect on experimental and clinical pain, which appears to be mediated locally and not by systemic absorption.¹¹ Topical application of ketorolac tromethamine for ankle sprain results in analgesia and reduced swelling superior to both placebo and oral administration of an NSAID¹² while resulting in plasma drug levels lower than those associated with oral administration of a 10 mg dose of ketorolac.

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Topical NSAIDs have also been evaluated for experimental gingivitis in humans,¹³ acute soft tissue injuries,¹⁴ and as a route of administration for rheumatoid arthritis.¹⁵

In this study, we evaluated the administration of ketoprofen in a proprietary gel formulation directly into surgical extraction sites following the removal of two impacted third molars to determine the analgesic efficacy and safety of peripheral administration. The results of three studies done in series provide evidence for a peripheral site of action, greater analgesia in comparison to the same dose given orally, and lower plasma drug levels suggestive of less potential for systemic toxicity.

METHODS

Subjects for this investigation were oral surgery outpatients undergoing the surgical removal of two mandibular impacted third molars with parenteral sedation and local anesthesia. The first two studies consisted of a single-dose, double-blind, parallel groups comparison to evaluate the analgesic efficacy of ketoprofen administered directly into the surgical site in comparison to a placebo control. A third open-label study evaluated the pharmacokinetic properties of the ketoprofen gel formulation in comparison to oral ketoprofen capsules. Subjects were 16 years of age or older, free of systemic disease, without history of psychiatric illness, and had no history of allergy to aspirin or NSAIDs. Additional exclusion criteria included concomitant medication with NSAIDs or antihistamines and pregnant or lactating females. Subjects were informed of possible risks of oral surgery and the investigational treatments and signed a consent form approved by the NIDR Institutional Review Board.

The first study compared suppression of postoperative pain with 10 mg and 30 mg doses of ketoprofen in a proprietary gel formulation to a placebo gel formulation when placed submucosally into the extraction sockets. Three groups were randomized to receive one of the following treatments: 10 mg ketoprofen gel, 30 mg ketoprofen gel, or placebo gel administered bilaterally into two mandibular extraction sites. The drugs were formulated such that 0.5 ml of the placebo, 0.5 ml of 1% ketoprofen gel, or 0.5 ml of 3% ketoprofen gel were administered into each extraction site for a total administered volume of 1.0 ml. The second study compared submucosal administration of 10 mg of drug at the site of injury to oral administration of the same dose and placebo administered both orally and at the surgical site. Three groups were randomized to receive either 0.5 ml of 1% ketoprofen gel into each extraction

socket (10 mg total dose) and 1 ml of the placebo gel swallowed, 1 ml of the active drug swallowed (10 mg dose) and the placebo submucosally, or the placebo via both routes. The third study was open-label to avoid the complexity of administering the placebo via three different routes of administration. Subjects were randomly allocated to receive either 10 mg ketoprofen administered into the two mandibular extraction sites, 10 mg ketoprofen placed topically onto the extraction sites, 10 mg ketoprofen gel formulation placed on the base of the tongue and swallowed, or a 25 mg ketoprofen oral capsule. Drug and placebo were supplied by the manufacturer (Block Drug Company, Jersey City, NJ) as identically appearing gel formulations randomly allocated by the NIH Pharmaceutical Development Service to consecutive subjects.

Two partial or full bony impacted mandibular teeth were extracted using 2% lidocaine with 1:100,000 epinephrine and intravenous sedation with midazolam. Primary closure was obtained using 3-0 chromic gut suture and gauze placed bilaterally. One hour postoperatively, patients were evaluated for hemostasis. Patients were excluded from participation if there was a lack of hemostasis or pain requiring immediate medication as reported by the patient. The drug formulations were administered by inserting a 14-gauge plastic catheter under the mucosal flap raised for the extraction and gently extruding 0.5 ml of the gel from a 1 ml tuberculin syringe. The gel formulation was administered orally by expressing the gel from a syringe onto the base of the tongue and having the patient swallow. In the first study, a custom acrylic stent was placed over the extraction sites for 1 hour to prevent leaking of the gel from the extraction sites. In the second study, gauze was placed bilaterally and held in place with firm biting pressure for 1 hour. Rescue analgesia was provided upon patient request consisting of either 100 mg of flurbiprofen p.o. for moderate pain or ketorolac 30 to 60 mg IM for severe pain.

Pain was rated at baseline, at 15 minutes postdrug, and at 30-minute intervals for up to 6 hours using a 100 mm visual analog scale (VAS) with anchors of *no pain* and *worst possible pain*. Duration of anesthesia was evaluated to ensure that postoperative pain was not influenced by residual mandibular anesthesia. Patients were instructed to tap their lower lip and categorize the sensation as normal (0), tingling (1), or numb (2). The presence of side effects was also evaluated at each observation.

Blood samples in the third study were collected into chilled, heparinized tubes prior to drug administration (0 time) and at 15, 30, 60, 90, 120, 150, 180, 240, 300, and 360 minutes following drug and centrifuged under

refrigeration (4°C). The plasma was decanted and frozen in dry ice for storage at -70°C until shipped on dry ice for analysis (Hazleton Wisconsin, Inc., Madison, WI). Ketoprofen plasma levels were measured following extraction of the drug and an internal standard into ethyl ether made acidic by the addition of potassium phosphate monobasic. The organic layer was evaporated to dryness and the residue reconstituted in the mobile phase prior to analysis by reversed-phase high-pressure liquid chromatography with ultraviolet absorbance detection.

Patients were contacted by telephone on the seventh postoperative day to evaluate the incidence of complications. In the first study, 34 patients underwent oral surgery as candidates for inclusion in the study. Four patients were not evaluated for the following reasons: only one observation after the offset of mandibular anesthesia (2), only one lower extraction done (1), and patient did not receive study drug (1). In the second study, 52 patients underwent oral surgery as candidates for inclusion in the study. Eight patients were not evaluable: persistent paresthesia (1 patient), confounding medication given intraoperatively (1 patient), excessive surgical difficulty with prolonged duration of surgery (1 patient), or requested rescue analgesic less than 1 hour after study drug administration (4 placebo patients, 1 ketoprofen in extraction site). A total of 51 patients were placed in the third study, with evaluable data from 50 subjects included in the analyses; 1 patient in the topical ketoprofen group was withdrawn from the study for treatment of persistent bleeding requiring local anesthesia administration and placement of an additional suture.

Pain intensity over the entire 6-hour observation period was evaluated by repeated measures analysis of variance. Post hoc comparison between treatment groups was based on the total pain scores for the entire 6 hours, as measured by a VAS (adjusted for the interval of the time period) using a one-way analysis of variance and Duncan's multiple-range test. The incidence of complications for the different routes of administration was compared by Fischer's exact test for groups collapsed across the three studies.

RESULTS

The duration of mandibular anesthesia was similar across groups, with virtually all patients reporting the return of normal sensation by 120 to 150 minutes from the end of surgery. Treatment groups were also similar for the doses of local anesthetic and midazolam, the difficulty of the surgical procedure, and demographic characteristics (Table I).

Pain onset in the first study occurred over the first 2 hours (Figure 1, upper panel). Pain intensity over the course of the 6-hour observation period was significantly different between the three drug groups ($F = 6.32$, $p < 0.01$), with mean pain intensity for the 10 mg ketoprofen group reaching a maximum on the VAS of one-third of the placebo group. Administration of 10 mg ketoprofen gel significantly suppressed the sum of the pain intensity values (Figure 1, lower panel) in comparison to the placebo gel ($p < 0.01$). Pain in the 30 mg ketoprofen group was less than the placebo over time but somewhat higher than the 10 mg group. The sum of the pain intensity scores, however, was also significantly less than the placebo ($p < 0.01$). There was no difference between the two doses of ketoprofen for the sum of the pain intensity scores.

To control for possible absorption from the site of administration at the surgical wound, a second study compared the 10 mg dose of ketoprofen given into the extraction sites or swallowed orally. The placebo resulted in pain, which increased over the first 2 to 3 hours postdrug administration to reach 70% of maximal levels (Figure 2, upper panel). Administration of 10 mg into the surgical sites significantly reduced total pain scores ($p < 0.01$) in comparison to placebo and oral administration of the same dose formulation (Figure 2, lower panel). Oral administration of the 10 mg ketoprofen formulation did not result in any significant difference in comparison to the placebo for the sum of the pain intensity values.

In the third open-label study, the plasma drug levels of ketoprofen resulting from administration at the surgical site were compared to oral administration of the same formulation, topical application of the gel formulation to the oral mucosa overlying the extraction sites, or oral administration of a 25 mg ketoprofen capsule. Plasma drug concentrations following oral ingestion of the 10 mg gel formulation were significantly elevated at the 15-minute blood sample in comparison to 10 mg at the surgical site, peaked at 30 minutes, and then gradually decreased over the remainder of the observation period (Figure 3). Administration of a standard 25 mg ketoprofen capsule resulted in a significantly greater plasma drug concentration than the 10 mg surgical site dose from 60 minutes postdrug to the last observation at 360 minutes. Topical administration of the 10 mg dose formulation resulted in plasma drug concentrations comparable to administration into the surgical site.

Adverse events reported across the three studies are summarized by route of administration in Table II. The incidence of postoperative bleeding, usually manifesting as an ooze from the extraction site, was similar

Table I Demographic and Surgical Characteristics of Study Sample for Each Study

	<i>n</i>	Age	Sex	Height (cm)	Weight (kg)	Midazolam Dose (mg)	Lidocaine Dose (mg)	Duration of Surgery (min)	Surgical Difficulty ^a
Study 1									
Placebo	10	18.9 ± 3.0	6 M 4 F	174.8 ± 8.1	68.1 ± 12.4	5.2 ± 1.0	110.4 ± 5.1	25.7 ± 5.5	3.7 ± 0.5
10 mg ketoprofen	10	23.4 ± 5.5	3 M 7 F	170.2 ± 9.4	66.6 ± 11.2	4.9 ± 0.3	114.2 ± 11.1	28.0 ± 7.9	3.8 ± 0.5
30 mg ketoprofen	10	21.2 ± 3.6	4 M 6 F	165.4 ± 10.4	65.3 ± 6.6	5.1 ± 0.7	124.8 ± 24.6	31.7 ± 12.9	3.7 ± 0.5
Study 2									
Placebo	8	18.5 ± 1.8	2 M 6 F	168.9 ± 8.9	65.8 ± 11.3	5.5 ± 1.4	211.5 ± 48.8	24.2 ± 7.9	3.9 ± 0.4
Ketoprofen surgical site	18	22.2 ± 5.3	3 M 15 F	164.1 ± 6.9	61.1 ± 10.6	5.4 ± 1.4	180.0 ± 40.9	28.5 ± 5.6	3.6 ± 0.5
Oral ketoprofen	18	21.2 ± 4.9	9 M 9 F	168.7 ± 10.4	64.4 ± 12.5	5.3 ± 1.3	188.9 ± 45.5	23.1 ± 7.1	3.8 ± 0.4
Study 3									
Oral ketoprofen	13	19.3 ± 3.0	6 M 6 F	165.9 ± 8.9	67.8 ± 12.0	3.8 ± 1.1	174.5 ± 43.7	15.8 ± 8.6	3.8 ± 0.4
Topical ketoprofen	12	19.1 ± 2.3	2 M 10 F	165.1 ± 12.0	69.0 ± 10.2	4.3 ± 0.8	177.0 ± 47.2	11.5 ± 6.8	3.5 ± 0.8
Ketoprofen surgical site	13	22.8 ± 4.3	2 M 11 F	163.7 ± 8.6	57.4 ± 9.2	4.0 ± 1.5	180.0 ± 38.9	13.0 ± 3.8	3.5 ± 0.6
Ketoprofen capsule	12	20.4 ± 3.7	4 M 8 F	168.3 ± 7.0	65.9 ± 7.3	4.0 ± 1.0	171.0 ± 55.6	14.9 ± 10.7	3.8 ± 0.6

a. Surgical difficulty classified as simple extraction (1), soft tissue impaction (2), partial bony impaction (3), and full bony impaction (4).

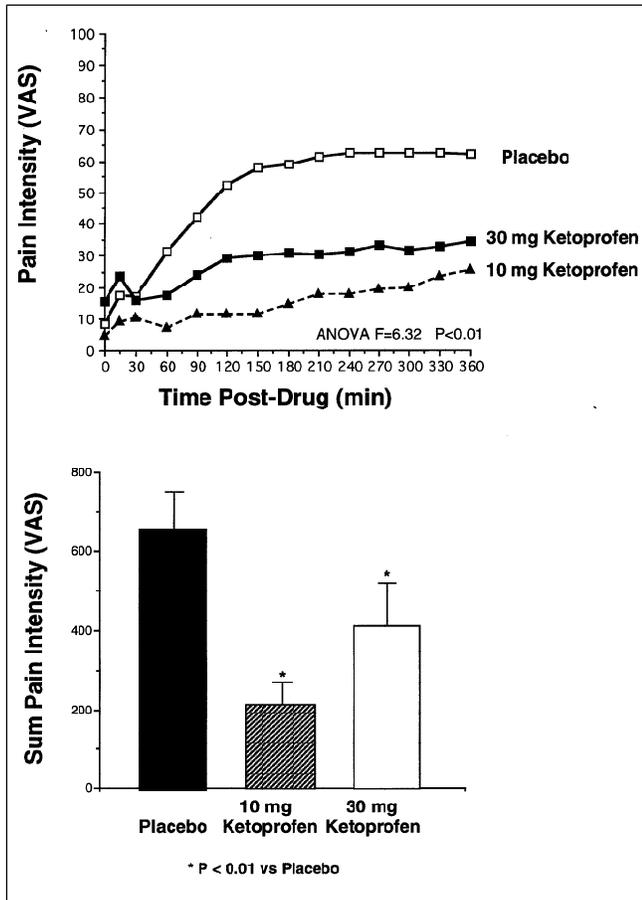


Figure 1. Pain intensity as measured by visual analog scale over time (upper panel) and the sum of pain intensity at all time points (lower panel) for placebo, 10 mg ketoprofen, or 30 mg ketoprofen applied to the surgical extraction sites.

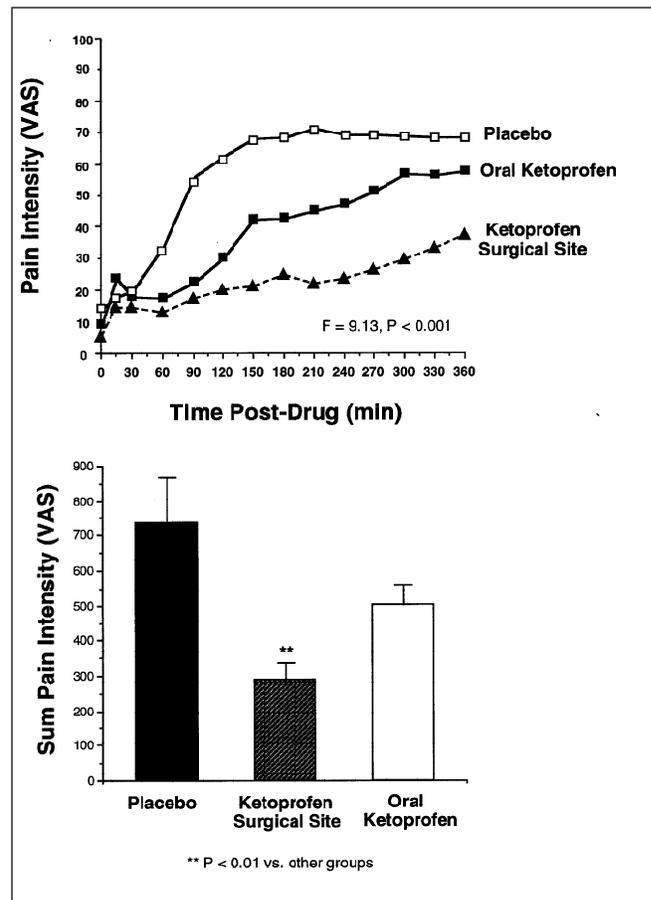


Figure 2. Pain intensity as measured by visual analog scale over time (upper panel) and the sum of pain intensity at all time points (lower panel) for placebo, 10 mg ketoprofen applied to the surgical extraction sites, or the same dose formulation placed on the tongue and swallowed.

across treatment groups, with ketoprofen administered into the surgical site (15%) having the identical rate of postoperative bleeding as oral ketoprofen (15%). The rate of infection was nonsignificantly elevated for both ketoprofen administered into the surgical site and for oral ketoprofen in comparison to the placebo. The incidence of impaired healing at the extraction site, characterized as alveolar osteitis, was similar across groups. Complications associated with the surgical procedure itself, such as persistent paresthesia to the lingual or mandibular nerve, were also similar in occurrence between treatment groups. Pain at the extraction site occurred more frequently following administration of ketoprofen at the surgical site, but the overall incidence (9%) was too low to differentiate statistically from administration of the placebo to the surgical site (3%). Other nonspecific adverse events such as drowsiness, dizziness, fatigue, nausea, and sore throat were reported equally across groups.

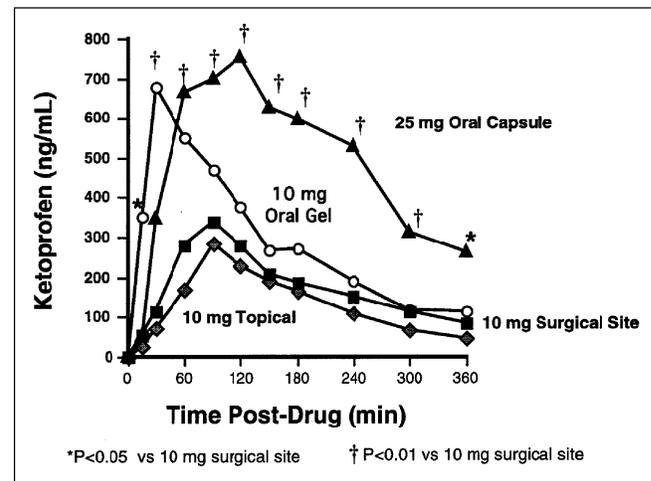


Figure 3. Plasma concentrations of ketoprofen following oral administration of a 25 mg ketoprofen capsule, 10 mg of ketoprofen gel administered orally, 10 mg ketoprofen gel placed into the surgical extraction site, or 10 mg ketoprofen gel topically administered over the extraction sites.

Table II Adverse Events Reported on Day of Surgery or at 7-Day Postsurgery Follow-Up

Treatment	<i>n</i>	None	Bleeding	Infection	Alveolar Osteitis	Paresthesia	Headache	Pain at Drug Administration	Other
Ketoprofen surgical site ^a	55	19	8 (15%)	10 (18%)	4 (7%)	2 (4%)	8 (15%)	5 (9%)	21 (38%)
Placebo surgical site ^b	22	13	3 (10%)	1 (3%)	1 (3%)	1 (3%)	2 (7%)	1 (3%)	6 (20%)
Ketoprofen topical	13	5	3 (23%)	1 (8%)	2 (15%)	1 (8%)	1 (8%)	0	3 (23%)
Ketoprofen oral ^c	47	19	7 (15%)	10 (21%) ^d	2 (4%)	4 (9%)	9 (19%)	0	18 (38%)

Includes all subjects exposed to drug. Multiple adverse events reported by some patients.

a. 10 mg or 30 mg doses from all three studies.

b. Placebo from first and second studies.

c. 10 mg or 25 mg doses from second and third studies.

d. $p < 0.05$ versus placebo surgical site.

DISCUSSION

Peripheral administration of a 10 mg formulation of ketoprofen was more effective than oral administration of the same dose, suggesting a local site of action. Absorption from the surgical wound and distribution to some other site of action would have resulted in analgesia comparable to the oral formulation. The greater analgesic effect with the peripheral route is presumably due to achieving a higher effective drug concentration at the site of injury without loss due to distribution to other compartments or the onset of elimination. The area under the drug concentration curve over the first 120 minutes indicates that a larger portion of the orally administered ketoprofen gel was in the circulation longer than the locally administered drug, suggesting a higher drug concentration at the surgical site for the peripherally administered ketoprofen. Topical administration of 10 mg of the ketoprofen gel formulation resulted in plasma drug levels similar to the same dose administered into the socket. While the efficacy of the topical formulation was not assessed in the third open-label study, it is likely that most of the administered drug was absorbed by the gauze that was placed over the extraction sites following local administration.

Administration of the ketoprofen 30 mg gel formulation in the first study resulted in greater analgesia than the placebo gel but demonstrated a trend toward less efficacy than the 10 mg dose. The small sample size for this dose range study magnified the effect of one subject in the 30 mg group who did not achieve relief with the locally applied drug and reported maximal pain intensity requiring remedication. The low mean levels of pain for the 10 mg dose, approximately 10-20 on 100 mm VAS for the first 5 hours, would have made it

difficult to demonstrate any greater analgesic effect for the 30 mg dose, even in the absence of this subject's data.

Ketoprofen, like other NSAIDs, interferes with the formation of products of the arachidonic acid cascade.¹⁶ However, assessment of ketoprofen's effect on a spinally mediated reflex in both normals and paraplegic patients is suggestive of a central site of action.¹⁷ Similarly, the antinociceptive actions of NSAIDs in the formalin test are 100 to 1000 times more potent when administered intrathecally in comparison to intraperitoneal administration,¹⁸ also suggestive of a central site of action for NSAID analgesia. The results of this study are supportive of a peripheral site of action but do not contradict a central site of action following systemic absorption and distribution. The slow time course of drug action in the oral surgery model under these conditions, in which the drug was given 60 to 90 minutes prior to the onset of pain as the effects of the local anesthetic dissipated, does not permit evaluation of any early effects of NSAIDs that might occur at central sites prior to the cumulation of a sufficient concentration in the periphery to inhibit prostaglandin formation.

A recent study in an oral surgery model demonstrated that oral administration of a high dose of flurbiprofen (200 mg) did not result in drug concentrations at the extraction sites exceeding the IC₅₀ dose for cyclooxygenase-2 activity until 90 minutes postdrug.¹⁹ Administration of a dose in the normal therapeutic range (50-100 mg) would likely have taken even longer to achieve inhibitory concentrations of cyclooxygenase-2 at the presumed site of action. Analgesic onset following oral administration of 25 to 100 mg flurbiprofen occurs as early as 30 minutes postdrug^{20,21} and is substantial by 60 minutes.²⁰⁻²² The early analgesic onset following oral administration of NSAIDs

such as fluribiprofen compared to the time course for achieving inhibitory concentrations in the periphery is suggestive of an early analgesic action at some other site, presumably the central nervous system. The ability of NSAIDs to suppress edema in the oral surgery model²³ and their well-documented effects in patients with rheumatoid arthritis are consistent with a peripheral site of anti-inflammatory action.

The administration of a drug with the ability to interfere with platelet adhesion into a surgical extraction site raises concerns regarding the potential for postoperative bleeding or interference with normal healing. By administering the ketoprofen gel formulation at 1 hour postsurgically, we were able to administer the drug following the establishment of a stable clot in the extraction sites yet prior to pain onset, which usually occurs 2 to 3 hours after surgery. The insertion of a catheter for administration of the gel initiated slight bleeding in most subjects, but visual observation of the extraction sites at 15-minute intervals did not reveal any signs of prolonged bleeding associated with the NSAID administration. Postoperative monitoring at 7 days also did not reveal any increase in the incidence of delayed healing, normally manifesting as an increased incidence of alveolar osteitis in oral surgery patients. These findings and the well-documented safety record for orally administered ketoprofen^{24,25} suggest that administration of this dose formulation is safe even when administered into a surgical wound.

The incidence of postoperative infections was elevated following administration of ketoprofen into the surgical site and orally, either as the 10 mg gel formulation or the 25 mg capsule. The rate of infection was substantially higher (18%-21%) than that normally seen in our clinic (approximately 5%) and was coincident with oral surgery performed by one less experienced resident among the six who performed surgery for this study. The similarity in the frequency of infection when ketoprofen was administered either orally or directly into the surgical site suggests that the elevated incidence of infection in these groups is not attributable to the placement of the drug into the extraction sites.

The renal and gastrointestinal adverse effects associated with NSAIDs are related to distribution to these sites as a consequence of the oral or parenteral routes of administration. While not directly assessed in this single-dose study, the demonstration of much lower drug levels for the locally administered drug formulation in comparison to a normal therapeutic dose of ketoprofen (25 mg) implies a decreased potential for drug toxicity. The plasma concentrations following administration into the surgical site were comparable

to topical administration of the drug formulation, a less efficient approach in the oral environment due to salivary dilution of the drug away from the site of administration and possible adhesion to the gauze placed over the extraction site following administration. The greater analgesic efficacy achieved by administration of the 10 mg dose into the surgical sites in comparison to oral administration of the same formulation resulted in lower blood concentrations predictive of less toxicity than the usual oral route of administration, likely by achieving higher drug concentrations at the site of intended drug action. No direct comparison was made of the bioavailability of the gel formulation to the oral capsule. The demonstration that the 10 mg gel formulation achieved approximately the same peak levels as the 25 mg capsule and resulted in mean plasma levels that were double the capsule at 30 minutes suggests that the gel formulation had comparable or greater bioavailability.

The results of this study provide a basis for the peripheral administration of NSAIDs such as ketoprofen in lower than usual doses to achieve efficacy comparable or greater than systemic administration. Administration to a surgical site was well tolerated, suggestive of tissue compatibility at other sites less disrupted than a fresh surgical wound. The lower blood concentrations seen following peripheral administration are also predictive of less toxicity at sites normally associated with NSAID toxicity, the kidneys and GI tract, although repeated dosing is needed to be comparable to chronic administration.

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