Evaluations of New Drugs

Ketoprofen: A Review of Its Pharmacologic and Clinical Properties

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Ketoprofen (Orudis), a highly potent and safe nonsteroidal antiinflammatory drug of the propionic acid derivative group, was synthesized in France by Rhône-Poulenc chemists in 1967, 3 years after the prototype ibuprofen. Ketoprofen was introduced in 1973 in France and the United Kingdom for antiinflammatory use. Today the drug is available in about 80 countries and has recently been approved in the United States for treatment of rheumatoid arthritis and osteoarthritis. The therapeutic experience with ketoprofen is estimated to have exceeded 3 million patient-years. Double-blind trials have established its therapeutic equivalence with aspirin, indomethacin, and ibuprofen in rheumatoid arthritis and with aspirin in osteoarthritis. Ketoprofen has a short half-life, a simple metabolism, and a broad therapeutic window, and does not accumulate with multiple doses. These features contribute to a rapid onset of action, flexible dosing, and a reliable tolerance profile.
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OUTLINE

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Ketoprofen is a nonsteroidal antiinflammatory drug (NSAID) belonging to the group of substituted 2-phenylpropionic acids. Its structural formula (2-(3-benzolphenyl)-propionic acid) is shown in Figure 1; its molecular weight is 254.29. Ketoprofen was synthesized by Rhône-Poulenc Research Laboratories, Paris, in 1967 and was first approved for clinical use in France and the United Kingdom in 1973. The drug is currently marketed throughout the world in a variety of forms: capsules, injectable solutions, suppositories, and a topical gel. A controlled-release capsule for once-daily administration (Oruvail) was introduced in the United Kingdom. Extensive testing in

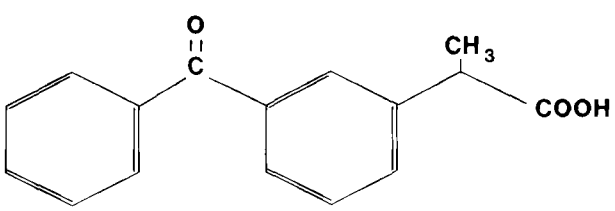

Figure 1. Structural formula of ketoprofen.

the United States, confirming foreign clinical experience, demonstrated that ketoprofen is effective in treatment of arthritis. Furthermore, the drug has a well-defined safety profile that offers significant advantages over aspirin in controlled studies. United States approval of clinical use of ketoprofen capsules in osteoarthritis and rheumatoid arthritis was granted in January 1986.

This review describes the pharmacology and pharmacokinetics of ketoprofen and summarizes the results of United States clinical trials conducted between 1975 and 1984. Both published and unpublished data are included to provide a comprehensive summary of the available information. The unpublished trials are being summarized for publications in a journal supplement; all of them have been subjected to review by the Food and Drug Administration. Several reviews of the foreign clinical studies with ketoprofen have been published.[1-4]

Pharmacology and Toxicology

Antiinflammatory Effects

In several animal models (rats, mice, rabbits, guinea pigs, and pigeons) ketoprofen displayed potent activity against acute inflammation (increased vascular permeability, edema, and erythema), subacute inflammation (pleurisy, abscess, and granuloma formation), and chronic inflammation (experimental arthritis and synovitis).[5-9] These tests showed ketoprofen to be 20 times more potent than ibuprofen, 80 times more potent than phenylbutazone, and 160 times more potent than aspirin in reducing inflammation from carrageenin-induced abscesses in rats.[8,9] The drug's potency was generally equivalent to that of indomethacin in most models.[5-9] Of significance, in rat adjuvant arthritis, the minimally effective dosage of ketoprofen (2.5 mg/kg/d) could be doubled to produce even greater efficacy (up to 70% inhibition), while a similar dosage increase with indomethacin resulted in 100% mortality.[5]

Analgesic and Antipyretic Effects

Ketoprofen was a potent, peripherally acting analgesic in 2 classic animal models of pain. In preventing pain from intraperitoneal injections of phenylbenzoquinone, it was equivalent to indomethacin and 70 times more potent than aspirin.[5] In Randall and Selitto's paw-compression test, ketoprofen was equivalent to indomethacin,[8] slightly more potent than naproxen,[8] and 30 times more potent than aspirin.[5] Like other NSAIDs, ketoprofen is inactive in assays measuring centrally mediated analgesia (e.g., tail pinching).[7] It did not reduce basal temperature, but decreased antigen-induced hyperthermia in rats and rabbits to a greater extent than any other NSAID tested, including indomethacin, naproxen, ibuprofen, and phenylbutazone.[7]

Mechanism of Action

As with all NSAIDs, the physiologic basis of ketoprofen's pharmacodynamic activities is presumed to be interference with arachidonic acid metabolism (Figure 2). Ketoprofen is one of the most powerful inhibitors of cyclo-oxygenase at concentrations well within the range of therapeutic plasma levels (EC_{50} 2 μg/L). The drug was 6 and 12 times more potent than naproxen and indomethacin respectively in inhibiting prostaglandin synthesis in isolated guinea pig lung preparations perfused with arachidonic acid.[9] Ibuprofen, phenylbutazone, and aspirin were 800–1500 times less potent than ketoprofen.[9] Although there was a much narrower range of relative potencies in antiinflammatory activity (carrageenin-induced abscess) among the NSAIDs tested, the rank order remained the same, indicating a correlation between prostaglandin synthesis inhibition and antiinflammatory activity.[9] Other studies showed potent inhibition of prostaglandin synthesis by ketoprofen in ram and rat seminal vesicle microsomes,[10,11] in rat and rabbit renal medulla,[12] and in human lung tissue.[11] Prostaglandin levels and associated paw edema after intraplantar carrageenin injections were also reduced by ketoprofen.[10]

In addition to its effects on cyclo-oxygenase, ketoprofen inhibits the lipoxygenase pathway of the arachidonic acid cascade.[11,13] This pathway produces noncyclized monohydroxy acids (HETE) and leukotrienes.[12] Of these, only leukotrienes (B_4, C_4, and D_4) are thought to increase vascular permeability[14]; however, both HETE and leukotrienes synthesized within leukocytes are active in promoting leukocyte migration and activation.[15-17] The clinical relevance of lipoxygenase inhibition remains to be established, but it has been suggested that lipoxygenase inhibitors may attenuate cell-mediated inflammation and thus retard the progression of tissue destruction in inflamed joints.[11]

In addition to these properties, ketoprofen has other pharmacologic effects that may be relevant to its antiinflammatory and analgesic activity. For exam-

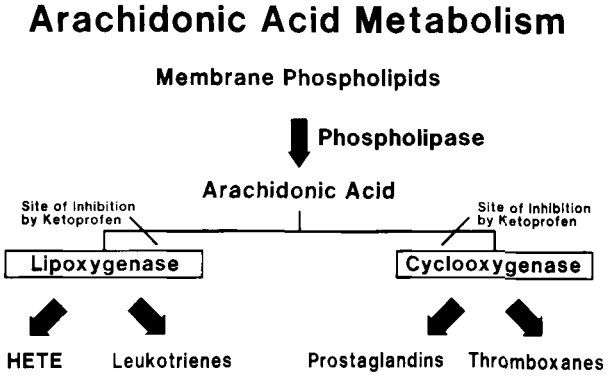

Figure 2. Schematic diagram of arachidonic acid metabolism.

ple, it is a powerful inhibitor of bradykinin,[7] an important chemical mediator of pain and inflammation. Also, it stabilizes lysosomal membranes against osmotic damage,[18] and prevents the release of lysosomal enzymes that mediate tissue destruction in inflammatory reactions.[19]

Toxicology

Acute oral toxic levels of ketoprofen (LD_{50}) ranged from 360–575 mg/kg in mice and from 56–160 mg/kg in young adult rats (Charles River, CD). In guinea pigs and dogs, oral LD_{50} values were greater than 1000 mg/kg.[8] Drug toxicity was characterized by sedation, adynamia, diarrhea, and emesis (dogs only); gastrointestinal lesions were present at autopsy.[8] Subacute toxicity studies using multiple doses were performed in several mammalian species. Maximum daily dosages for studies of at least 1 year in duration were 12.5 mg/kg/day in rats, 27 mg/kg/day in baboons, and 32 mg/kg/day in mice.[8] By comparison, the recommended dosage for humans (maximum daily dose 300 mg) is 4.3 mg/kg/day (70-kg human). Rats exhibited toxic effects in the gastrointestinal and renal systems, a spectrum consistent with the typical NSAID profile.[8] Dogs were also highly sensitive to gastrointestinal effects; however, baboons had only minimal irritation of the gastrointestinal tract.[8]

There was no evidence of carcinogenicity or mutagenicity in standard screening assays, and the drug appeared to have no effect on protein, or on DNA or RNA synthesis (unpublished data on file at Ives Laboratories, New York, NY). No embryotoxic or teratogenic effects have been demonstrated for ketoprofen and the drug has not been shown to affect fetal or postpartum development.[8] As with other NSAIDs, its use during pregnancy should be avoided since increased maternal toxicity and dystocic effects have been observed in rats.

Clinical Pharmacology

Pharmacokinetics and Metabolism

Human pharmacokinetic studies showed that orally administered ketoprofen is rapidly absorbed, metabolized, and excreted. Absorption is more than 90% complete[20]; peak plasma levels are reached within 1–2 hours in most subjects.[21] Total bioavailability (AUC) is dose proportional in the range of 75–200 mg. The plasma half-life is approximately 2 hours in healthy young volunteers.[21] Ketoprofen concentrations in the synovial fluid peak approximately 2 hours after the peak plasma levels and decrease more slowly, so that synovial fluid levels exceed plasma levels from 4 hours after dosing.[22]

In the blood stream, ketoprofen is 99% bound to protein (mostly albumin).[23] The drug follows a simple metabolic pathway (primarily glucuronidation), leading to the formation of an unstable glucuronic ester that is excreted in the urine.[24] Conjugation and renal excretion are somewhat delayed in elderly subjects (65 years of age or older),[25,26] resulting in an increase of the terminal half-life to 3–5 hours. Measurements of the area under the curve after multiple dosing show that this half-life is short enough to prevent toxic accumulation of the drug in elderly patients with rheumatoid arthritis.[22] Thus no routine dosage adjustment seems to be necessary in these persons.

A similar minor prolongation in half-life was seen in patients with impaired renal function (creatinine clearance 20–60 ml/min)[27] or alcoholic cirrhosis.[28] In patients with renal dysfunction, a close correlation between creatinine clearance and ketoprofen clearance was observed. Even among these patient populations, the risk of excessive drug accumulation is low.

Clinical evidence indicates that ketoprofen's effect may be of longer duration than expected on the basis of the short plasma half-life. It is routinely prescribed on a twice-daily regimen, particularly in Great Britain. Double-blind trials demonstrated that its antiinflammatory activity when taken twice daily at 50–150 mg per dose (except in juvenile rheumatoid arthritis, in which it is 25 mg twice a day) is comparable to that of piroxicam 20 mg/daily,[29] indomethacin 50 mg twice daily,[30] and Distalgesic (d-propoxyphene 65 mg plus acetaminophen 650 mg) 4 times a day[31] in osteoarthritis; diclofenac 50 mg twice a day in rheumatoid arthritis[32]; indomethacin 25 mg twice a day in juvenile rheumatoid arthritis[33]; benoxaprofen 600 mg daily in ankylosing spondylitis[34]; and ibuprofen 400 mg 3 times a day in a mixed arthritic population.[35] Delayed clearance from the synovial fluid, as mentioned above, or possibly a prolonged effect on mediators of inflammation may underlie these clinical results.

Drug Interactions

Despite being 99% protein bound,[23] ketoprofen does not appear to alter the pharmacokinetics of other highly protein-bound drugs such as oral antidiabetic agents[36] or anticoagulants.[37,38] Single-dose bioavailability was unchanged when ketoprofen was given with food or with antacid.[39,40] In addition, no clinically significant interactions were detected between ketoprofen and digoxin[41] or hydrochlorothiazide (pharmacodynamic assessments after 4 days of dosing in both studies). Concurrent administration of aspirin reduced protein binding of ketoprofen, but this was offset by accelerated plasma clearance.[42] Although these offsetting effects resulted in no net change in the plasma concentration of free ketoprofen, the complex nature of the kinetic interaction might lead to unpredictable individual variations. Therefore coadministration with aspirin is not recommended. Concurrent administration of ketoprofen did not affect salicylate pharmacokinetics; however, probenecid reduced both protein binding and clearance of ketoprofen.[43] The latter appeared to be secondary to inhibition of glucuronidation of ketoprofen and probenecid, both of which are transformed

Table 1. Ketoprofen in Osteoarthritis

Efficacy variables	Score Improvement from Baseline at First Visit (%)[a] KET vs PLA[b] K 200 (n = 26)	K 300 (n = 25)	PLA (n = 29)	KET vs PLA[c] K 200 (n = 55)	K 300 (n = 67)	PLA (n = 55)	KET vs ASA K 200 (n = 38)	ASA (n = 38)
Morning pain	20.2[d]	22.3[d]	6.3	18.9[e]	25.5[e]	−0.4	23.7	12.9
Walking pain	27.6[d]	30.0[d]	8.9	19.3[e]	26.2[e]	7.1	25.4	12.7
Night pain	31.4[f]	14.0	15.8	16.2	29.2[f]	15.9	22.6	16.0
Pain index (on examination)	37.2	42.3	21.9	46.4[d]	46.0[d]	26.5	30.5	28.7

[a]First visit was after 1 week of treatment.
[b]Four-week trial.
[c]Six-week trial.
[d]$p < 0.01$ versus control treatment.
[e]$p < 0.001$ versus control treatment.
[f]$p < 0.05$ versus control treatment.
K 200 = ketoprofen 200 mg/d; K 300 = ketoprofen 300 mg/d; PLA = placebo; ASA = aspirin.
From references 45–47.

by the same biochemical pathway. Consequently, combined treatment with these agents should be avoided.

Thyss et al[44] described several cases of impaired clearance of methotrexate and serious toxic, even fatal, consequences after coadministration with ketoprofen or diclofenac. Reduced clearance of methotrexate at high doses has been known in association with aspirin[45] or indomethacin.[46] It appears to be a class phenomenon related to inhibitory effects of NSAIDs on renal prostaglandins. With growing use of methotrexate as a remittive agent in rheumatoid arthritis, the risk of this potentially life-threatening interaction should receive wide recognition.

Clinical Efficacy

Osteoarthritis

Ketoprofen was compared to placebo or aspirin in 3 separate double-blind, parallel trials in the United States. (In all double-blind studies, control agents were given in capsule form rather than any commercial tablet preparation; therefore aspirin was neither coated nor buffered.) The placebo-controlled trials involved 301 patients and had a duration of 4 and 6 weeks.[47,48] The aspirin-controlled trial involved 85 patients and lasted 12 weeks.[49] Ketoprofen doses were 200 or 300 mg/day in the placebo-controlled trials and 200 mg/day in the aspirin-controlled trial.

Within 1 week of treatment in each trial, ketoprofen provided relief from the painful symptoms of osteoarthritis (Table 1). Relief was sustained over the entire course of each trial. In both placebo-controlled trials, ketoprofen was significantly superior to placebo in global assessments both by patients and investigators (Table 2) and in reducing walking pain and joint tenderness after 1 week of treatment. In both trials, the rate of dropouts for lack of efficacy was significantly lower and the percentage of patients with marked or moderate improvement at the final visits were significantly higher in the ketoprofen group. No significant differences were found between the responses of patients receiving the 200 and 300 mg daily doses of ketoprofen.

Compared to aspirin 2600 mg/day, ketoprofen 200 mg/day was significantly superior in controlling both walking pain and morning pain at week 12. Aspirin did not have any statistically significant advantages over ketoprofen. The percentages of patients with marked or moderate improvement at the last visit were similar in both groups, whether patients' ratings (71% for ketoprofen; 67% for ASA) or investigators' (67% for ketoprofen; 63% for ASA) were considered.

Rheumatoid Arthritis

Separate studies compared ketoprofen to placebo,[50] aspirin,[51] indomethacin,[52] and ibuprofen[53] in

Table 2. Global Assessment of Improvement in Osteoarthritis at End of Treatment

Duration of study (wks)	Assessment by	Percentage Improved (markedly or moderately) Ketoprofen 200 mg/d (n)	Ketoprofen 300 mg/d (n)	Placebo (n)	Aspirin (n)
4[45]		(32)	(32)	(35)	—
	Observer	72[a]	72[a]	51	—
	Patient	72[b]	78[c]	46	—
6[46]		(63)	(70)	(66)	—
	Observer	54[a]	60[a]	32	—
	Patient	52	61[a]	35	—
12[47]		(42)	—	—	(43)
	Observer	67	—	—	63
	Patient	71	—	—	67

[a]$p < 0.05$.
[b]$p < 0.01$.
[c]$p < 0.1$.
Probability values show significance versus control group (chi-square test across 5 classes of improvement: marked, moderate, minimal, none, and worse).

Table 3. Ketoprofen in Rheumatoid Arthritis

Efficacy variables	Score Improvement from Baseline at First Visit (%)[a] KET vs PLA K 200 (n = 85)	K 300 (n = 87)	PLA (n = 83)	KET vs ASA K 200 (n = 87)	ASA (n = 81)	KET vs IND KET (n = 64)	IND (n = 63)
Swollen joint index	35.1[b]	30.0[b]	18.4	11.4	10.8	37.8[c]	23.2
Tender joint index	43.1[b]	42.3[b]	26.0	25.4	25.9	34.2	35.5
Number of tender joints (moderate and severe)	48.6[b]	45.4[b]	23.4	40.4	37.2	45.8	55.5
Global assessment by physician	20.0[d]	19.5[d]	7.5	27.2	21.6	30.1	25.8
Global assessment by patient	21.4[d]	22.5[d]	5.2	26.2	26.4	27.8	22.5

[a]The first visit was at 2 weeks in the aspirin-controlled study, at 1 week in the other 2 trials.
[b]$p < 0.01$ vs control treatment.
[c]$p < 0.05$ vs control treatment.
[d]$p < 0.001$ vs control treatment.
K 200 = ketoprofen 200 mg/d; K 300 = ketoprofen 300 mg/d; KET = ketoprofen at variable doses; IND = indomethacin; PLA = placebo; ASA = aspirin.

rheumatoid arthritis using a double-blind, parallel design. In each trial the patients were required to meet American Rheumatism Association (ARA) criteria for active disease after a pretrial washout period. Disease-modifying antiarthritic agents (e.g., gold salts, antimalarials) were permitted provided the dosage remained constant throughout the study.

Ketoprofen provided rapid, long-lasting relief from pain and swelling. In most variables, it was both clinically and statistically superior to placebo[50] and equivalent to aspirin[51] and indomethacin.[52] Table 3 shows the results obtained at the first visit in 5 key variables in 3 trials in rheumatoid arthritis; ketoprofen-treated patients had significant reductions from baseline in the number of tender and swollen joints. Symptomatic relief was maintained over the course of each trial (6–54 wks).

Each study analyzed patients having a predetermined degree of improvement at the last visit in 4 selected variables (global assessments by patients and investigators, duration of morning stiffness, and grip strength). At the last visit, ketoprofen had a statistically significant advantage in both global assessments and in duration of morning stiffness when compared to placebo, and there was a trend toward superiority for ketoprofen in grip strength ($p < 0.09$).[50] When compared to indomethacin, a significantly greater percentage of patients showed global improvement (investigator's rating) at the last visit (82% vs 66%; $p < 0.05$).[52] Patients' global ratings also showed a trend toward superiority for ketoprofen (68% vs 52%; $p < 0.08$).

As expected, the number of dropouts for lack of efficacy was significantly greater for placebo than for ketoprofen.[50] In the indomethacin trial, there were more dropouts for lack of efficacy in the indomethacin group (18.6%) than in the ketoprofen group (11.6%).[52]

Significantly more patients in the aspirin group dropped out due to adverse reactions (28.1% vs 12.2%; $p < 0.01$), indicating that ketoprofen has a wider therapeutic margin than aspirin.[51] Troublesome side effects from aspirin included gastrointestinal disturbances and salicylism (mostly tinnitus and hearing impairment). In one placebo comparison, the ketoprofen dosage was either 200 or 300 mg/day. No statistically significant differences in efficacy were observed between these levels, tested in 85 and 87 patients respectively.[50] It is therefore recommended that dosing be initiated at 225 mg/day; individual patients may benefit from adding a fourth capsule to reach the recommended maximum of 300 mg/day. The dosing recommendations for rheumatoid arthritis and osteoarthritis do not differ.

In the flexible-dose trials, the mean dose of ketoprofen was approximately 240 mg/day; most patients used either 200 or 300 mg/day. The dose ratios for the active controls were 16.4:1 for aspirin and 1:2 for indomethacin. The ratio for aspirin was lower than the scheduled 18:1, probably because side effects prevented patients in the aspirin group from reaching the maximum dose permitted in the protocol (5.4 g/d).

Ketoprofen was compared with ibuprofen in 103 patients.[53] The results of this double-blind, parallel study showed comparable efficacy for both drugs, with ketoprofen having a slight therapeutic advantage in mean score differences and in the percentage of patients improved according to global self-assessment at the last visit (53% for ketoprofen vs 41% for ibuprofen). The mean dose of ketoprofen was 225 mg/day and that of ibuprofen was 1717 mg/day. Gastrointestinal side effects were comparable in both groups; however, dizziness was reported more frequently by the ibuprofen-treated patients.

Ketoprofen was tested in the United States in 4 additional indications, for which the marketing approval has not yet been granted.

Ankylosing Spondylitis

Ketoprofen 200–300 mg/day (mean dose 245

mg/d) was compared to indomethacin 75–150 mg/day (mean dose 116 mg/d) in a double-blind crossover trial involving 57 patients.[54] The treatment period for each drug was 8 weeks and there was a drug-free washout period between the limbs of the study. Patients were not crossed over to the alternate drug until they had suffered a well-defined flare in symptoms.

Ketoprofen reduced mean pains scores by 50% or more in all pain variables and reduced the duration of morning stiffness from 3 hours to 1 hour. Improvement was close to maximum after the first week of treatment, particularly with respect to spontaneous pain values and the investigator's global assessment. No statistically significant differences between ketoprofen and indomethacin were noted.

Acute Gouty Arthritis

The 59 patients chosen for the multicenter study[55] demonstrated acute involvement of 1 or 2 joints, with onset of inflammation less than 48 hours prior to enrollment and adequate initial severity of inflammation. They were randomly assigned to either ketoprofen 150 mg loading dose, then 100 mg 3 times a day or indomethacin 75 mg loading dose, then 50 mg 3 times a day for 7 days. Pain, tenderness, restriction of motion, swelling, and redness were evaluated for each affected joint. In addition, a global assessment of each affected joint was made by patients and investigators.

Acute gout attacks were rapidly and effectively controlled by both drugs. The mean total score was reduced from 12.63 to 5.60 by ketoprofen on day 2 of treatment. Both treatment groups produced statistically significant improvement compared to baseline on days 2, 5, and 8. The results produced by indomethacin were clinically and statistically indistinguishable from those produced by ketoprofen.

Acute Painful Shoulder Syndrome

The results of an open-label trial in 23 patients with bursitis or tendinitis indicated that ketoprofen provided rapid and effective symptomatic relief in both conditions.[56] Improvements in joint mobility and onset of pain relief were noted on day 1 of treatment by 82% of patients. At the end of treatment (7 days), 100% of the patients gave ketoprofen a good or very good global assessment.

Juvenile Rheumatoid Arthritis

The Pediatric Rheumatology Collaborative Study Group performed a 4-week open-label pilot study in 35 children with JRA. Ketoprofen was administered at doses increasing from 100–200 mg/m^2/day. Global improvement was noted in 62% by the observers and in 68% by parents.[57] No double-blind pediatric studies have been performed in the United States; therefore, the use of ketoprofen in children is not recommended.

Clinical Safety

In United States clinical trials, the safety of ketoprofen was statistically evaluated in a total of 1545 patients, of whom 978 were treated in double-blind trials. The comparatively benign side-effect profile seen was as expected from the vast foreign experience with the drug. The United States data were analyzed[58] (data on file, Ives Laboratories) to address areas of particular interest, such as safety in the elderly, effects on kidneys and liver, associations of adverse drug reactions (ADR) with duration of treatment, or concomitant medications. No unusual reactions or disturbing patterns were noted in this analysis, which also included the events deemed unrelated to trial treatments. No deaths were attributed to ketoprofen in the United States trials.

Most of the ketoprofen ADR were mild upper gastrointestinal complaints such as nausea, dyspepsia, or epigastric discomfort. Less frequent were subjective nervous system symptoms (headache, drowsiness, dizziness) and complaints referable to the lower gastrointestinal tract (diarrhea, constipation, flatulence). Treatment was discontinued for side effects in 13% of patients. Table 4 shows the most common side effects in the United States trials for ketoprofen, 2 active controls (aspirin and indomethacin), and placebo (before grouping; see footnote, Table 3).

In aspirin-controlled studies, aspirin produced significantly more adverse effects than ketoprofen. When ADR were grouped into mutually related categories such as upper and lower gastrointestinal distress, the following ADR groups were significantly more frequent in aspirin-treated patients: upper gastrointestinal distress ($p < 0.01$), salicylism ($p < 0.001$), rash ($p < 0.05$), pruritus ($p < 0.05$), upper respiratory inflammation ($p < 0.05$), and weight gain ($p < 0.05$). Compared to placebo, only upper gastrointestinal (13.2% vs 21.9%) and lower gastrointestinal distress (1.6% vs 5.0%) were significantly more frequent in patients receiving ketoprofen. No statistically significant difference was found in the frequency of any ADR between ketoprofen and either ibuprofen or indomethacin.

Examination of the safety data for serious gastrointestinal reactions in all patients treated with ketoprofen (excluding single-dose and short-term clinical pharmacologic studies) (data on file, Ives Laboratories) revealed that peptic ulcer occurred in 2% (40 of 1987 patients), including cases of dubious causality. Gastrointestinal hemorrhage without an identified ulcer occurred in 14 patients. Serious gastrointestinal complications (peptic ulcer, melena) were more frequent among the aspirin-treated patients (1.76%) than those receiving ketoprofen (0.35%) in the matched populations. These observations dovetail with the results of studies showing more frequent and more severe pathologic changes on gastroscopic examination[59] and greater loss of radiolabeled red blood cells from the gastrointestinal tract of aspirin-

Table 4. Most Frequent Side Effects in Double-blind United States Trials

Adverse reactions	Patients with ADR (%) Orudis (n = 700)	Aspirin (n = 197)	Indomethacin (n = 122)	Placebo (n = 203)
CNS/sensory				
Dizziness	3.6	6.6	5.7	1.5
Headache	9.3	7.6	27.0	5.4
Tinnitus	2.3	24.9	2.5	2.0
Gastrointestinal				
Anorexia	3.0	1.5	0.8	2.0
Heartburn	2.9	6.1	4.1	1.5
Miscellaneous burning	2.9	8.1	—	1.0
Indigestion	2.4	6.1	1.6	2.0
Epigastric distress	1.4	3.7	1.6	—
Stomach upset	0.9	5.6	0.8	0.5
Dyspepsia	0.9	1.0	3.3	—
Nausea	9.7	15.7	10.7	5.4
Epigastric pain	3.6	13.2	1.6	2.0
Abdominal pain	6.7	7.6	4.9	1.0
Constipation	3.6	7.6	8.2	8.4
Diarrhea	5.0	4.6	8.2	8.4
Flatulence	3.6	6.6	1.6	1.5
Skin				
Rash, nonspecific	2.1	6.6	0.8	3.0
General				
Edema, peripheral	2.1	1.5	0.8	0.5

For the purpose of overall statistical analysis, some of the above forms were grouped; e.g., upper gastrointestinal distress cluster consisted of reports of nausea, heartburn, indigestion, epigastric pain, or distress (see text).
From reference 57.

treated patients.[60,61] Moreover, dropouts for gastrointestinal ADR were more frequent in the aspirin group in aspirin-controlled trials in rheumatoid arthritis (ketoprofen 6.1%, ASA 12.3%)[50] and osteoarthritis (ketoprofen 4.8%, ASA 7.0%).[48]

Transient depression of renal function (increased blood urea nitrogen [BUN] and serum creatinine; fluid retention) is characteristic of NSAIDs.[62] Since prostaglandins synthesized in the kidneys are potent vasodilators that serve to balance the effects of vasoconstrictive stimuli (norepinephrine, angiotensin II, renin) on renal blood flow,[63–65] preventing their production will affect renal function in some situations. As expected, the presence of underlying pathologic conditions that cause renal ischemia, such as congestive heart failure, high renin state, cirrhosis, and renal disease, predispose patients to adverse renal effects during NSAID treatment.[62,66] Elderly patients receiving concomitant diuretic treatment are also susceptible.[66] Renal functional changes induced by NSAIDs, whether asymptomatic or accompanied by edema, are reversible on withdrawal of the drug.[66]

In the ketoprofen group, these transient renal effects were observed in 7.9% of patients with and in 2.9% of patients without concomitant diuretic therapy ($p < 0.05$). Transient azotemia was reversible within 2 weeks of discontinuing ketoprofen. Three of 1987 patients had treatment suspended for BUN and serum creatinine increases. Elevations in serum creatinine were much less frequent than increases in BUN. It was significant that patients with existing mild renal dysfunction did not experience further deterioration in most instances (data on file, Ives Laboratories).

Much less common but more severe nephrotoxic reactions that can be associated with NSAIDs are interstitial nephritis and renal papillary necrosis.[62] The etiology of this syndrome is not clearly defined; however, it has been postulated that prostaglandin deficiency may lead to an unchecked hypersensitivity reaction in susceptible individuals.[67] No cases of organic renal injury were observed in the United States trials with ketoprofen and only two cases of interstitial nephritis related to ketoprofen have been reported in the literature. One patient had a combination of tubular necrosis, interstitial nephritis, and duodenal ulcer after 4 days of taking ketoprofen 100 mg/d intramuscularly, which resolved after a brief course of dialysis.[68] The second case involved a kidney that had been transplanted 7 years prior to the incident.[69] The patient was receiving a triamterene-hydrochlorothiazide combination in addition to ketoprofen; thus the relationship of the adverse effect to ketoprofen is questionable. This patient had to be maintained on dialysis indefinitely.

In view of the experience with benoxaprofen, it is germane to point out that no evidence of hepatotoxicity related to ketoprofen was discovered in an exhaustive review of laboratory and clinical data compiled in the United States clinical trials.[70] In one patient with an episode of reversible increase in

transaminases, a causal role for ketoprofen could not be ruled out. The time course indicated that concomitant estrogen treatment was a more likely cause. Moreover, reviews of the literature[71,72] stated that no cases of liver injury attributable to ketoprofen have been reported. European postmarketing surveillance identified several nonfatal cases of jaundice or abnormal liver function tests, but no firm causal relationships were established and information on alternative causes is lacking.

Similarly, no anaphylactoid or severe allergic complications were observed in the United States trials.[58] Foreign clinical data demonstrated cross-sensitivity to ketoprofen and other NSAIDs among aspirin-intolerant patients,[73] including one fatal case.[74] The so-called aspirin-intolerance syndrome (bronchospasm, urticaria, rhinitis) is presumably pharmacologically rather than immunologically mediated.[75]

No significant age-dependent relationships were evident in the analysis of safety data.[58] Similarly, significant relationships between dose and adverse reactions were not demonstrated except for upper gastrointestinal distress, which was significantly more frequent at 300 than at 200 mg/day (data on file, Ives Laboratories). Adverse drug reactions did not appear to be time dependent, particularly in the case of peptic ulcers and gastrointestinal hemorrhage, both of which occurred randomly throughout the time course (data on file, Ives Laboratories). Thus no type of ADR was identified that seemed to reflect cumulative effects of the drug. Patients receiving concomitant corticosteroid therapy had a significantly higher frequency of upper gastrointestinal distress than those receiving only ketoprofen (14.3% vs 5.5%). As stated above, patients receiving concomitant diuretics had a higher frequency of edema and transient elevation of BUN or creatinine levels than those receiving only ketoprofen.[58]

Further evidence of the low toxicity of ketoprofen comes from the National Poison Information Service of the United Kingdom and Ireland.[76] In acute overdose with ketoprofen, no symptoms at all were observed in 16 of 20 patients despite ingestion of up to 5 g. Vomiting was recorded in three patients and transient drowsiness in another; no fatalities were reported. Human toxic levels for ketoprofen remain unknown.

Conclusions

Ketoprofen (Orudis) is a nonsteroidal antiinflammatory agent with rapid onset of action and a short plasma half-life. It ranks among the most potent inhibitors of the cyclo-oxygenase pathway of arachidonic acid cascade, and inhibits lipoxygenase as well. Clinical testing in the United States demonstrated that ketoprofen is comparable in efficacy to aspirin in osteoarthritis and rheumatoid arthritis; to indomethacin in rheumatoid arthritis, ankylosing spondylitis, and acute gout; and to ibuprofen in rheumatoid arthritis. Improvement in arthritis variables was noted in pivotal studies after 1 week of treatment and was sustained throughout the trials (6–54 wks). Osteoarthritis and rheumatoid arthritis are presently the only approved indications.

After extensive patient usage over 13 years, ketoprofen has a reliable safety profile. Review of extensive data from United States clinical trials confirmed the foreign experience. Compared to aspirin, ketoprofen produced significantly fewer gastrointestinal side effects and serious gastrointestinal complications. Significant liver toxicity appears to be absent with ketoprofen, and organic renal injury is rare. Reversible renal functional changes, with or without edema, were seen with ketoprofen as with other drugs of this class, but were rarely of clinical concern. Ketoprofen appears to have a low potential for allergic manifestations, aside from cross-reactivity in aspirin-intolerant patients, which is a pharmacologically mediated feature of prostaglandin synthetase inhibitors.

With a short half-life in the elderly as well as in young adults, ketoprofen rapidly achieves steady state in plasma and synovial fluid and provides prompt therapeutic action. Also, it is promptly cleared on termination of treatment. Testing has shown good clinical tolerance in the elderly and even in patients with impaired renal and hepatic function.

Ketoprofen has entered the United States scene after a hiatus of 4 years since the approval of diflunisal, piroxicam, and benoxaprofen and since the ban of the latter. It seems very appropriate that a harbinger of a "new generation" (though "new" only in the regulatory sense) is a drug well known and long used abroad, and one with a aura of predictability.

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Commentaries

Commentary 1

There seems little doubt that ketoprofen is both safe and efficacious as an anti-inflammatory analgesic. There is some question in my mind as to its advantages over other available products. Studies comparing ketoprofen with indomethacin, ibuprofen, and other newer non-steroidal anti-inflammatory analgesics have not shown any noteworthy improvement in therapeutic effect. All of the inhibitors of cyclo-oxygenase must share, to a greater or lesser degree, the same group of pharmacologic effects. The toxicity (GI, CNS, renal, hematologic), and not the efficacy, is the usual limiting factor in treatment. In most controlled trials, GI intolerance is the most frequent reason for discontinuation of treatment. The propionic acid derivatives (ibuprofen, naproxen, fenoprofen, and ketoprofen) all produce about 5 to 15% incidence of gastrointestinal complaints, but these symptoms are usually less severe than those produced by aspirin or indomethacin. The incidence of other toxic effects appears to be similar within this group, and all of these drugs are better tolerated than aspirin.

So why pick ketoprofen? The short half-life may or may not be an advantage (less accumulation but lower patient compliance). We already have nonsteroidal analgesics with short (ibuprofen), medium (naproxen), and long (piroxicam) half-lives. The European safety data are encouraging, since ketoprofen seems to be relatively free of serious immunologic, renal, hepatic, or bone marrow toxicity. Also encouraging is the fact that reported cases of overdose have not been life-threatening. Finally, cost will have to be considered a big disadvantage since ibuprofen is available inexpensively without prescription.

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Commentary 2

Nonsteroidal antiinflammatory drugs (NSAIDs) continue to play a significant role in the treatment of many rheumatic diseases. Currently, there are 13 non-salicylate NSAIDs marketed in the United States with the promise of more to be released in the future. Although these agents have proven efficacy in rheumatic disease, limitations to their use are evident. Significant side effects occur with these drugs including gastrointestinal disturbances, renal disorders, and CNS effects. In addition, variability in patient response is a well recognized phenomenon associated with these agents.[1–3] Therefore, trials of several different NSAIDs in individual patients are encouraged to attain optimal therapeutic response.

To date, none of the NSAIDs available has proven clearly superior to any other in the treatment of rheumatoid or osteoarthritis. Thus, caution is warranted in evaluating new NSAIDs. When commenting on the burgeoning number of these drugs Kraag[4] suggested that ". . . we should analyze the literature critically before readily prescribing a drug whose only advantage may be that it is new." In examining the available data pertinent to ketoprofen, this word of caution seems appropriate.

Ketoprofen is the latest addition to the propionic acid derivatives which include ibuprofen, fenoprofen and naproxen. It has been utilized extensively in Europe and has recently been released in the United States. Dr. Kantor has presented data from US studies to support ketoprofen's efficacy in rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and gout. Evaluations of ketoprofen's therapeutic effectiveness indicate it is more effective than placebo and similar in efficacy to aspirin and other NSAIDs. Evidence from foreign studies support these results.[5–8] The most interesting aspect of ketoprofen's activity is the potential for dosage regimen flexibility. The plasma half-life of ketoprofen is only 2 hours and the usual recommended dosing regimen is three to four times daily. It has been suggested, however, that ketoprofen's long synovial fluid half-life may be a more useful guide to the time course of action of the drug.[9] Accordingly, some initial studies indicate that this drug may be efficacious when given in a twice daily regimen.[8,10,11] Thus, a potential advantage of ketoprofen could be a prolonged efficacy with less drug accumulation and therefore decreased toxicity when compared to twice daily agents with longer plasma half lives. This, however, has yet to be proven. Clearly, further evaluations of ketoprofen's effi-