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CCC: 0377-8282/2001

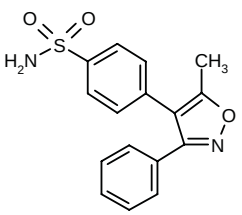
Valdecoxib and Parecoxib Sodium

Analgesic
Antiarthritic
Cyclooxygenase-2 Inhibitor

Valdecoxib
Prop INN; USAN

4-(5-Methyl-3-phenylisoxazol-4-yl)benzenesulfonamide

SC-65872



$C_{16}H_{14}N_2O_3S$ Mol wt: 314.3660

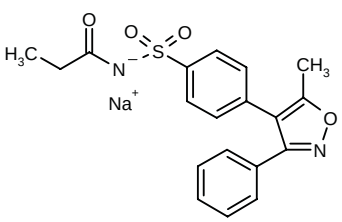
CAS: 181695-72-7

EN: 241522

Parecoxib Sodium
Prop INN, USAN

N-[4-(5-Methyl-3-phenylisoxazol-4-yl)phenylsulfonyl]propionamide sodium salt

SC-69124A



$C_{19}H_{17}N_2NaO_4S$ Mol wt: 392.4093

CAS: 198470-85-8
CAS: 198470-84-7 (as free acid)

EN: 258759

Synthesis of Valdecoxib

Treatment of deoxybenzoin (I) with hydroxylamine hydrochloride under basic conditions, NaOAc in EtOH/water or KOH/EtOH in toluene, gives the corresponding oxime (II). Deprotonation of oxime (II) with butyllithium in THF, followed by condensation with ethyl acetate or acetic anhydride, provides the isoxazoline (III), which is finally treated with cold chlorosulfonic acid followed by reaction of the intermediate sulfonyl chloride with aqueous ammonia (1-3). Scheme 1.

Description

M.p 172-3 °C.

Synthesis of Parecoxib Sodium

The acylation of 4-(5-methyl-3-phenylisoxazol-4-yl)-benzenesulfonamide, valdecoxib (I), with propionic anhydride (II) by means of TEA and DMAP in THF gives *N*-[4-(5-methyl-3-phenylisoxazol-4-yl)phenylsulfonyl]propionamide (III), which is then treated with NaOH in ethanol (4, 5). Scheme 2.

Description

Crystals, m.p. 271.5-2.7 °C.

Introduction

Aspirin has been widely used as an antipyretic and as a treatment for pain since the synthesis of acetylsalicylic acid (aspirin) in 1897. However, gastrotoxic actions were reported with use and later demonstrated in 1938 by endoscopic studies, indicating that aspirin produces lesions and ulcers in the gastric mucosa (6). Thus, a search for aspirin-like or nonsteroidal antiinflammatory drugs (NSAIDs) free of gastrotoxic effects was initiated. Over the last 30 years, approximately 20 NSAIDs have

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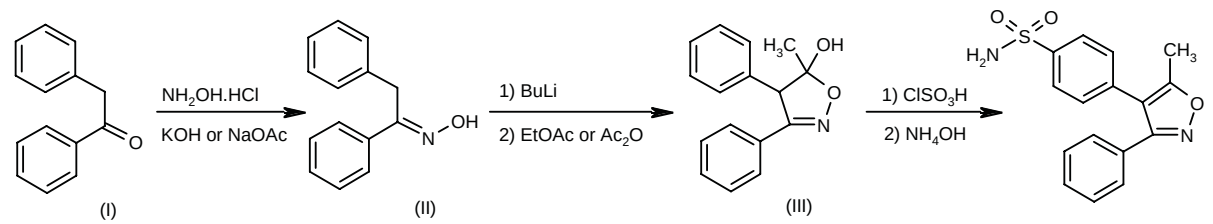
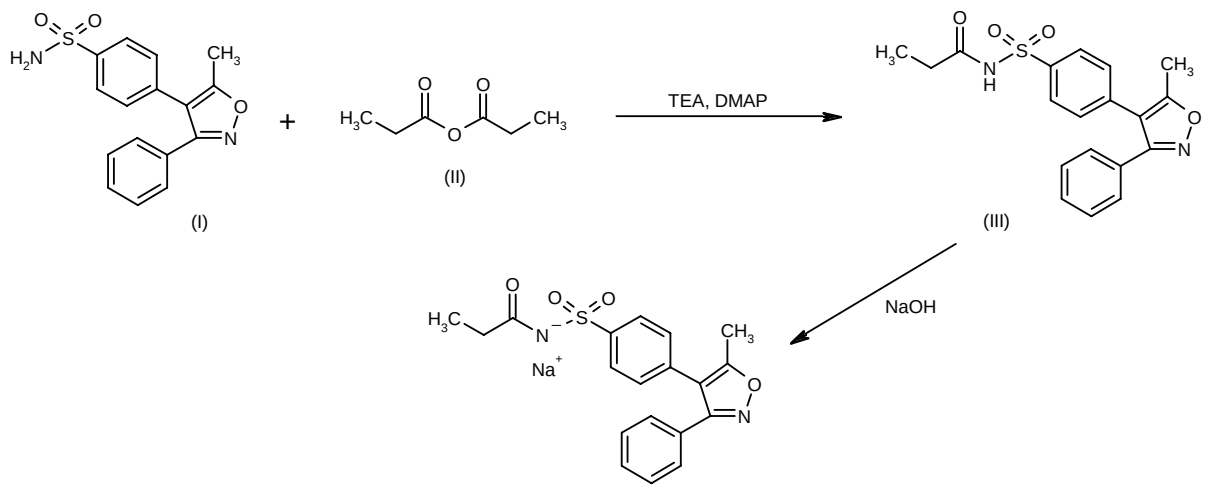
Scheme 1: Synthesis of Valdecoxib



Scheme 2: Synthesis of Parecoxib Sodium



entered the market although none of them are free of gastrotoxic effects and, in fact, the incidence of hospital referrals for ulcer complications has increased since the mid-1960s (7).

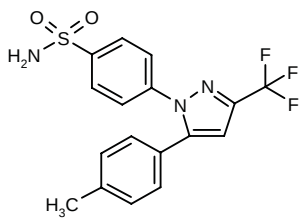
The search for specific cyclooxygenase-2 (COX-2) inhibitors has progressed extensively throughout the years, leading to the discovery and development of new generation NSAIDs such as celecoxib which was found to be an effective treatment of arthritis inflammation and pain with an improved safety profile in comparison to other conventional NSAIDs. Continued research has implicated COX-2 in a variety of other systems, including tumorigenesis and neural degeneration. Thus, the search for new NSAIDS continues in an attempt to address specific clinical needs. Table I shows the chemical structures of those COX-2 inhibitors launched or under development.

One existing critical clinical requirement is the need for a COX-2 inhibitor for parenteral use, as in postsurgical acute pain. Improved patient satisfaction, faster recovery and reduced complications can result from effective acute pain management (8). When pain treatment is inadequate the result can be mortality and morbidity, long-lasting psychological effects, anxiety, severe fatigue, delirium and adverse hemodynamic changes. Myocardial ischemia may develop due to tachycardia, hypertension and increased systemic resistance. Moreover, pulmonary complications such as atelectasis, pneumonia and hypoxia can result as a consequence of impaired ventilation and a patient's immune system may become suppressed (8-10).

Since the discovery of parenteral formulations of ketorolac, NSAIDs have been employed more and more often in the treatment of acute pain. NSAIDs present different adverse effects as compared to opiates; they do not induce respiratory depression, sedation or nausea and vomiting (11). Unfortunately, some available NSAIDs such as ketorolac can cause peptic ulcers, gastrointestinal hemorrhage, renal dysfunction, liver dysfunction and inhibition of platelet function possibly leading to increased operative bleeding (12-14). However, the more specific the NSAID is in inhibiting COX-2, the less influence it has on the COX-1 isoform and the lower the risk for induction of gastrointestinal side effects (15). Thus, the goal of

Table I: Selective COX-2 inhibitors launched or under development (Prous Science R&D Drug Backgrounders database).

Drug Name	Company	Indication	Status
1. Celecoxib (*Celebrex*)	Pharmacia/Pfizer/Yamanouchi	Rheumatoid arthritis, osteoarthritis, familial adenomatous polyposis	Launched 1999
2. Rofecoxib (*Vioxx*)	Merck & Co.	Rheumatoid arthritis, primary dysmenorrhea, acute pain	Launched 1999
3. Parecoxib sodium	Pharmacia/Yamanouchi	Pain	Preregistered
4. COX-189*	Novartis	Rheumatoid arthritis, osteoarthritis, pain	Phase III
5. Etoricoxib	Merck & Co.	Rheumatoid arthritis, osteoarthritis, pain	Phase III
6. Valdecoxib	Pharmacia/Pfizer/Yamanouchi	Arthritis, pain	Phase III
7. JTE-522	Japan Tobacco/R.W. Johnson	Rheumatoid arthritis, osteoarthritis	Phase II
8. ABT-963*	Abbott	–	Phase I
9. CS-502*	Sankyo	–	Phase I
10. FR-228352	Fujisawa	–	Preclinical
11. UR-8813*	Uriach	–	Preclinical



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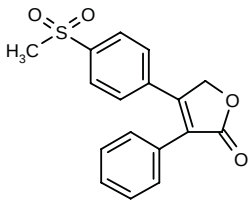

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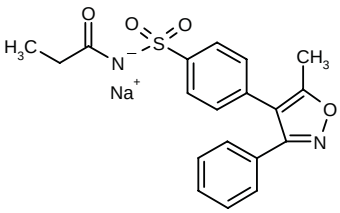

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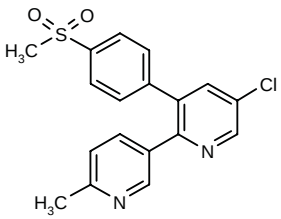

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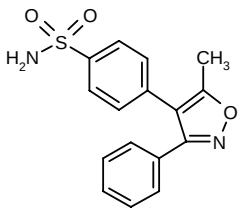

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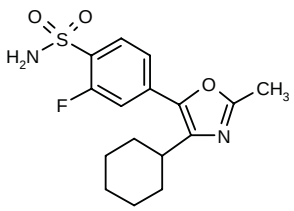

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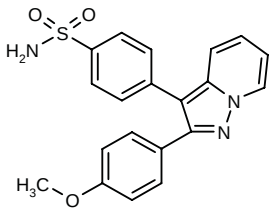

(10)

*Structure not yet detected

researchers in the search for effective NSAIDs for pain management is the development of a specific COX-2 inhibitor that can be administered intravenously and also possesses a superior safety profile over ketorolac. Agents such as celecoxib, which are highly COX-2 specific and have shown excellent efficacy in relieving inflammation and associated pain, unfortunately exhibit only modest aqueous solubility, thus restricting dosing options. In fact, very few NSAIDs can be administered parenterally.

In an attempt to overcome the solubility restriction, researchers at Searle have employed the prodrug approach. The result has been the discovery of the prodrug of a sulfonamide-based inhibitor, valdecoxib. The prodrug, parecoxib sodium, is rapidly converted to valdecoxib and has demonstrated potent antiinflammatory and analgesic activity. Parecoxib sodium has been selected for further development (5).

Pharmacological Actions

Valdecoxib potently and selectively inhibited a recombinant human COX-2 isoform with an IC_{50} value of

Table II: Pharmacokinetics of parecoxib sodium after single i.v. and i.m. administration (5, 16-21) (Prous Science PKline database).

Humans/animal species	Route of administration	Dose (mg)	t_{max}[a] (h)	$t_{1/2}$ (min)	V_d (l/kg)
Humans (M)	i.m.	1-40	1.1-3.5	15-35	–
Humans (M)	i.v.	1-200	0.27-2	5	–
Rats (M)	i.v.	12.5	–	8.4 ± 0.2	–
Dogs (F)	i.v.	12.5	–	33.2 ± 0.5	–
Monkeys (F)	i.v.	12.5	–	72.6 ± 0.24	–
Rats (M)	i.v.	12.5	–	–	< 0.6
Rats (F)	i.v.	5.0	–	–	< 0.6

[a]Value for valdecoxib. M = male; F = female

0.005 μM as compared to a value of 140 μM obtained for a recombinant human COX-1 isoform (1). The prodrug of valdecoxib, parecoxib sodium, was found to be rapidly converted to valdecoxib in *in vitro* studies using human liver microsomes and in *in vivo* studies conducted in rodents, dogs and monkeys (5).

Parecoxib sodium exhibited potent acute and chronic antiinflammatory activity in rats, as demonstrated in the carrageenan air pouch model, where 98% of inhibition was achieved with the dose of 0.3 mg/kg, and in the adjuvant arthritis model (ED_{50} = 0.08 mg/kg). Moreover, parecoxib sodium exhibited strong analgesic activity in carrageenan-induced paw edema in rats, where it was found to almost completely reverse hyperalgesia within 1 h after administration of the 30 mg/kg i.v. dose (ED_{50} = 5 mg/kg) (5).

Pharmacokinetic studies indicated that parecoxib sodium completely and rapidly converted in valdecoxib (see below), with bioequivalence found between parenterally administered parecoxib sodium and orally administered valdecoxib. In fact, oral valdecoxib showed antiinflammatory activity comparable to that of parenteral parecoxib sodium both in carrageenan-induced foot pad edema (ED_{50} = 10.2 mg/kg) and in rat adjuvant-induced arthritis (ED_{50} = 0.032 mg/kg). Moreover, valdecoxib was found to block prostaglandin production at the inflammatory site in the rat carrageenan air pouch model (ED_{50} = 0.05 mg/kg) (1).

Pharmacokinetics

Pharmacokinetic studies of parecoxib sodium were performed in rats, dogs, cynomolgus monkeys and humans (Table II). Intravenous administration of parecoxib sodium to all animal species resulted in complete and rapid conversion to valdecoxib with mean elimination $t_{1/2}$ values of 0.135 ± 0.003, 0.553 ± .009 and 1.21 ± 0.004 h, respectively (5).

A study using male and female rats showed no sex-related differences in $t_{1/2}$ or clearance values following administration of 5 mg/kg i.v. of parecoxib sodum. Results also showed that the agent was not extensively distributed to tissue since a volume of distribution of < 0.6 l/kg was obtained. Analysis of plasma following parecoxib sodium dosing revealed that the active drug valdecoxib was metabolized to a hydroxylated metabolite (M1) in plasma (16).

A randomized, double-blind, placebo-controlled, multiple-dose, parallel-group study reported the pharmacokinetics of parecoxib sodium (50 mg i.v. as a single dose on day 1, every 12 h on days 3-9 and a single morning dose on day 10) in healthy volunteers. Parecoxib sodium was rapidly converted to valdecoxib (elimination $t_{1/2}$ = 0.69 h) with peak plasma levels reached 30 min after parecoxib sodium dosing and steady state achieved on day 7. Peak M1 levels were seen about 1 h after parecoxib sodium dosing and steady state was achieved on day 7. The ratios of mean AUC values (day 10 AUC_{0-12}/day 1 $AUC_{0-\infty}$) for parecoxib sodium, valdecoxib and M1 were 1.03, 1.18 and 0.96, respectively, with linear pharmacokinetics obtained for all compounds. Parecoxib sodium was well tolerated with no clinically significant adverse events observed in this study (17).

The pharmacokinetics and tolerability of single-dose parecoxib sodium administered i.m. (1, 2, 5, 10, 20 or 40 mg) or i.v. (1, 2, 5, 10, 20, 50, 100 or 200 mg) were examined in 2 randomized, double-blind, placebo-controlled studies in 56 and 62 adult (mean ages 27.3-27.6 years) males, respectively. All doses were well tolerated with the maximum tolerated doses (MTDs) following i.m. and i.v. administered concluded to be at least 40 and 200 mg, respectively. Plasma concentrations of parecoxib sodium decreased rapidly following i.m. and i.v. administration, with apparent elimination $t_{1/2}$ values of 15-35 and 5 min, respectively. Valdecoxib t_{max} values were approximately 1.1-3.5 h after i.m. dosing and ranged from 16 min to 2 h following i.v. dosing. $AUC_{0-\infty}$ and C_{max} values for valdecoxib were dose-proportional with i.m. dosing and C_{max} values for valdecoxib were dose-proportional following i.v. administration. No pain at injection site was observed following i.m. administration and no serious or dose-dependent adverse effects were observed with either administration route (18, 19) (Boxes 1 and 2).

The pharmacokinetics of i.m. (1, 2, 5, 10 and 20 mg) and i.v. (1, 2, 5, 10, 20, 50 and 100 mg) parecoxib sodium were also evaluated in patients with postoperative pain following dental surgery. Both studies revealed that the C_{max} and AUC values increased dose-proportionately. The t_{max} following i.v. administration was 0.5 h for all doses (20, 21).

Box 1: Tolerability and pharmacokinetics of parecoxib following intramuscular administration (18) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled, dose-finding clinical study
Population	Healthy adult males (n = 56)
Treatments	Parecoxib, 1 mg i.m. s.d. Parecoxib, 2 mg i.m. s.d. Parecoxib, 5 mg i.m. s.d. Parecoxib, 10 mg i.m. s.d. Parecoxib, 20 mg i.m. s.d. Parecoxib, 40 mg i.m. s.d. Placebo
Conclusions	Parecoxib was safe in healthy adult males. The maximum tolerated single i.m. dose was 40 mg

Box 2: Tolerability and pharmacokinetics of parecoxib following intravenous administration (19) [Prous Science CSline database].

Design	Randomized, double-blind, placebo-controlled, dose-finding clinical study
Population	Healthy adult males (n = 62)
Treatments	Parecoxib, 1 mg i.v. s.d. Parecoxib, 2 mg i.v. s.d. Parecoxib, 5 mg i.v. s.d. Parecoxib, 10 mg i.v. s.d. Parecoxib, 20 mg i.v. s.d. Parecoxib, 50 mg i.v. s.d. Parecoxib, 100 mg i.v. s.d. Parecoxib, 200 mg i.v. s.d. Placebo
Conclusions	Parecoxib was safe in healthy adult males. The maximum tolerated single i.v. dose was 200 mg

Box 3: Gastroduodenal effects of parecoxib in the elderly (20) [Prous Science CSline database].

Design	Comparative, randomized, double-blind, placebo-controlled clinical study
Population	Healthy volunteers aged 65-75 y (n = 94)
Treatments	Parecoxib, 40 mg i.v. b.i.d. x 7 d (n = 31) Ketorolac, 15 mg i.v. q.i.d. x 7 d (n = 31) Placebo (n = 32)
Results	Rate of patients with gastroduodenal ulcers (%): K (23) > P (0) = Pl (0) [p <0.05] gastric ulcers (%): K (16) > P (0) = Pl (0) [p <0.05] duodenal ulcers (%): K (6) > P (0) = Pl (0) [p <0.05] gastric erosion or ulcers (%): K (90) > P (14) ≥ Pl (6) [p <0.05] duodenal erosion or ulcers (%): K (45) > P (10) ≥ Pl (0) [p <0.05]
Conclusions	Parecoxib was safer than ketorolac in healthy elderly volunteers

Clinical Studies

A randomized, double-blind, placebo-controlled, 7-day study evaluated the gastroduodenal effects of parecoxib sodium (40 mg b.i.d. i.v.) as compared to ketorolac (15 mg q.i.d. i.v.) in 94 elderly (65-75 years), healthy subjects. No significant differences were found in results from upper gastrointestinal patient endoscopies between the placebo and parecoxib sodium groups. However, the incidence of gastroduodenal (23%) and gastric (16%) ulcers was significantly increased in the group receiving ketorolac as compared to the parecoxib sodium and placebo groups (both 0%); the incidence of duodenal ulcers tended to be higher in the ketorolac group (6 *vs.* 0% for both parecoxib sodium and placebo). The incidence of gastric (90%) and duodenal (45%) erosion/ulcer incidence was also significantly greater in the ketorolac group as compared parecoxib sodium (14 and 10%, respectively) and placebo (0 and 10%, respectively). Ketorolac-induced damage was observed after only 5 days (20) (Box 3).

Box 4: Analgesic efficacy of parecoxib in postgynecologic surgery patients (21) [Prous Science CSline database].

Design	Comparative, multicenter, randomized, double-blind, placebo-controlled clinical study
Population	Patients undergoing elective abdominal hysterectomy or myomectomy, with moderate to severe pain
Treatments	Parecoxib, 20 mg i.v. s.d. Parecoxib, 40 mg i.v. s.d. Ketorolac, 30 mg s.d. Morphine sulphate, 4 mg s.d. Placebo
Results	Time to onset of perceptible pain relief (range, min): overall (6-13) Time to onset of analgesia (range, min): overall (10-23) Time to rescue medication (range, h): P (6-6.5) = K (6-6.5) > M (2.6) > Pl (1.8)
Conclusions	Parecoxib and ketorolac were more effective than morphine sulphate in moderate to severe pain following elective abdominal hysterectomy or myomectomy

Box 5: Analgesic efficacy of parecoxib in patients with postoperative dental pain (22) [Prous Science CSline database].

Design	Randomized, comparative, double-blind, placebo-controlled clinical study
Population	Patients undergoing extraction of two impacted third molars including bony resection (n = 304)
Treatments	Parecoxib, 20 mg i.v. s.d. Parecoxib, 40 mg i.v. s.d. Parecoxib, 20 mg i.m. s.d. Parecoxib, 40 mg i.m. s.d. Ketorolac, 60 mg i.m. s.d. Placebo
Results	Median time to onset of analgesia @ 0.25 h: Pim = Piv = K > Pl; @ 24 h: Pim = Piv = K > Pl Median time to perceptible pain relief @ 0.25 h: Pim = Piv = K > Pl; @ 24 h: Pim = Piv = K > Pl Maximal pain relief: Pim = Piv = K Duration of analgesia: P40 > P20 = K
Conclusions	Parecoxib 20 mg and 40 mg and ketorolac 60 mg had similar efficacy in pain following extraction of two impacted third molars

The analgesic efficacy of parecoxib sodium (20 or 40 mg i.v.) over morphine sulfate (4 mg i.v.) was shown in a randomized, multicenter, double-blind, placebo-controlled study also comparing the activity of ketorolac (30 mg i.v.). Women undergoing elective abdominal hysterectomy or myomectomy under general anesthesia and receiving PCA opioid until postsurgical day 1 participated in the trial. All groups showed similar mean times to onset of perceptible pain relief (6-13 min) and onset of analgesia (10-23 min). The mean times to rescue medication for parecoxib sodium and ketorolac (6-6.5 h) were similar and significantly greater as compared to morphine sulfate (2 h 26 min) and placebo (1 h and 50 min). Similar efficacy for all time-specific variables was observed for the parecoxib sodium and ketorolac groups. Parecoxib sodium was significantly superior to morphine sulfate and placebo at all times after the first 30 min of treatment (21) (Box 4).

The analgesic efficacy of parecoxib sodium in patients with postoperative dental pain has been demonstrated in a number of trials. A randomized, single-dose, double-blind, placebo-controlled study involving 304 patients experiencing moderate to severe pain following extraction of 2 impacted molars (including bony resection) compared parecoxib sodium (20 and 40 mg i.v. or i.m.) with ketorolac (60 mg i.m.). Similar efficacy was obtained for parecoxib sodium regardless of the route of administration. Patients receiving parecoxib sodium and ketorolac displayed similar median times to onset of analgesia or perceptible pain relief; maximum pain relief was also similar in these 2 groups. Parecoxib sodium was significantly superior to placebo in analgesic efficacy at all time points from 0.25-24 h. The duration of analgesia achieved with 40 mg parecoxib sodium was significantly longer as compared to 20 mg parecoxib sodium and ketorolac, which were not significantly different. No serious adverse events were observed with any treatment (22) (Box 5).

Similar results were obtained in 2 pharmacokinetic studies comparing the efficacy of parecoxib sodium administered i.m. (1, 2, 5, 10 and 20 mg) or i.v. (1, 2, 5, 10, 20, 50 and 100 mg) with ketortolac (30 mg i.m. or i.v.) in patients with postoperative dental pain (23, 24).

Results from the study involving i.m. administration showed that 20 mg parecoxib sodium and ketorolac were

Box 6: Pharmacokinetics and efficacy of intramuscular parecoxib in postoperative dental pain (23) [Prous Science CSline database].

Design	Comparative, placebo-controlled, dose-finding clinical study
Population	Patients with pain following third molar surgery
Treatments	Parecoxib, 1 mg i.m. s.d. Parecoxib, 2 mg i.m. s.d. Parecoxib, 5 mg i.m. s.d. Parecoxib, 10 mg i.m. s.d. Parecoxib, 20 mg i.m. s.d. Ketorolac, 30 mg i.m. s.d. Placebo
Results	Time to onset of pain relief (h): Pl* (>24) = P1* (>24) = P5* (>24) > P2* (1.83) > P10* (0.41) > K (0.23) = P20 (0.23) [*p <0.05 *vs.* K and P20] Time to rescue medication (h): K (8.0) ≥ P20 (7.68) > Pl = P1 Rate of patients not requiring rescue medication (%) @ 24 h: P20 (34) > other treatments (8-16)
Conclusions	Ketorolac 30 mg and parecoxib 20 mg had similar efficacy in dental pain

Box 7: Pharmacokinetics and efficacy of intravenous parecoxib in postsurgical dental pain (24) [Prous Science CSline database].

Design	Comparative, placebo-controlled, randomized, double-blind, dose-finding clinical study
Population	Patients with pain following third molar surgery
Treatments	Parecoxib, 1 mg i.v. s.d. Parecoxib, 2 mg i.v. s.d. Parecoxib, 5 mg i.v. s.d. Parecoxib, 10 mg i.v. s.d. Parecoxib, 20 mg i.v. s.d. Parecoxib, 50 mg i.v. s.d. Parecoxib, 100 mg i.v. s.d. Ketorolac, 30 mg i.v. s.d. Placebo
Results	Time to onset of pain relief (h): Pl* (>24) = P1* (>24) = P2* (>24) > P10* (0.43) ≥ P5* (0.35) ≥ K (0.23) ≥ P20* (0.18) = P50* (0.18) ≥ P100* (0.15) Time to rescue medication (h): P100 (13.5) ≥ P50 (10.5) ≥ P20 (8.0) ≥ K (7.83) Rate of patients not requiring rescue medication (%) @ 24 h: P100 (45.1) ≥ P50 (43.1) ≥ P20 (20.0) ≥ P5 (19.6) ≥ Pl, P1, P2, P10 [2-9.8]
Conclusions	Ketorolac and parecoxib 20 mg (or higher) were effective in dental pain

significantly superior in terms of time to onset of pain relief (14 min for both agents *vs.* 24 h, > 24 h, 110 min, > 24 h and 25 min for placebo, 1, 2, 5 and 10 mg parecoxib sodium, respectively) and time to rescue medication (7 h 41 min and 8 h 2 min for parecoxib sodium and ketorolac, respectively) as compared to all other groups; the 20 mg parecoxib sodium and ketorolac groups were not significantly different from each other. Parecoxib sodium was well tolerated with no serious or unexpected adverse events (23) (Box 6).

Results from the trial employing i.v. administration showed that all treatment groups were superior to placebo in terms of pain intensity difference, pain relief and sum of pain intensity difference and pain relief (PRID) with the exception of 1 and 2 mg parecoxib sodium on time to pain relief, which were similar to placebo (> 24 h *vs.* 12, 21, 26, 11, 11 and 9 min for ketorolac, parecoxib 5, 10, 20, 50 and 100 mg, respectively); similar patterns were obtained for times to perceptible and meaningful pain relief. Significantly longer times to rescue medication were obtained for 50 (10 h 34 min) and 100 (13 h 32 min) mg parecoxib sodium as compared to the other treatments. No significant difference was observed between the 20 mg parecoxib sodium groups and ketorolac in terms of time to rescue medication (8 h 2 min and 7 h 53 min). Moreover, the percentage of patients not requiring rescue medication over a 24 h period was higher for the 5, 20, 50 and 100 mg parecoxib sodium groups (19.6, 20, 43.1 and 45.1%, respectively) as compared to the ketorolac, placebo and 1 and 2 mg parecoxib sodium groups (2-9.8%) (24) (Box 7).

Valdecoxib is under phase III clinical studies as an oral treatment for osteoarthritis, rheumatoid arthritis and pain. Parecoxib sodium has been submitted for approval to the FDA for the management of acute pain and can be administered intramuscularly or intravenously. Valdecoxib

is under codevelopment by Pharmacia and Pfizer in the U.S. and is licensed to Yamanouchi in Japan, and parecoxib sodium is being developed by Pharmacia and is also licensed to Yamanouchi (25-28).

Manufacturer

Pharmacia Corp. (US), in codevelopment with Pfizer Corp. (US) and licensed to Yamanouchi Pharmaceutical Co., Ltd. (JP).

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