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Parecoxib (Parecoxib Sodium)

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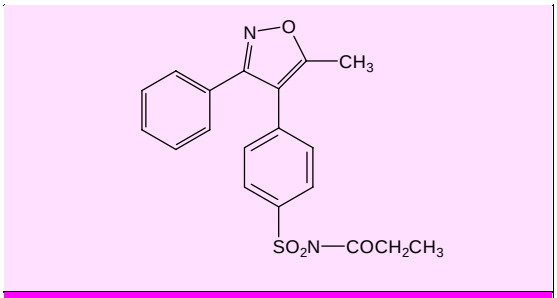
Abstract

▲ Parecoxib (parecoxib sodium) is an injectable prodrug of valdecoxib, which is a potent and selective inhibitor of cyclo-oxygenase-2.
▲ Intravenous (IV) or intramuscular (IM) parecoxib ≥20mg has analgesic activity superior to that of placebo and similar to that of IV or IM ketorolac 30 or 60mg in well controlled trials in patients with postoperative dental pain (n = 304 to 457).
▲ In a well controlled trial (n = 202), IV parecoxib 20 or 40mg showed analgesic activity greater than that of placebo and IV morphine 4mg and similar to that of IV ketorolac 30mg following gynaecological surgery.
▲ Following orthopaedic surgery, the analgesic activity of IV parecoxib 20 or 40mg was similar to that of IV ketorolac 30mg and superior to that of IV morphine 4mg or placebo in well controlled trials (n = 175 and 208).
▲ IV parecoxib (40mg twice daily for 7 days) produced significantly fewer gastrointestinal erosions and/or ulcers than ketorolac (15mg 4 times a day for 5 days) in healthy volunteers in a well controlled trial; effects on upper gastrointestinal mucosa were similar for parecoxib and placebo.
▲ Parecoxib is well tolerated after dental, gynaecological or orthopaedic surgery. The most common adverse events irrespective of treatment (parecoxib, ketorolac or placebo) after dental surgery were nausea, alveolar osteitis, dizziness and headache.
▲ Nausea, abdominal pain, headache, abdominal fullness, dizziness, back pain, fever, hypoactive bowel sounds, vomiting, tachycardia, somnolence, abnormal breath sounds and pruritus occurred in ≥10% of parecoxib recipients after gynaecological surgery. Similar results were seen in placebo recipients.

Features and properties of parecoxib (SC-69124A)		
Indications		
Moderate to severe acute pain		
Mechanism of action		
Analgesic	Prodrug of the cyclo-oxygenase-2 inhibitor valdecoxib	
Dosage and administration		
Usual dosage in clinical trials	Single dose 20 or 40mg	
Route of administration	Intravenous or intramuscular	
Pharmacokinetic profile for parecoxib 20mg in patients postsurgery unless stated otherwise		
	Intravenous	Intramuscular
Peak plasma concentration (valdecoxib)	0.45 mg/L	0.39 mg/L
Time to peak plasma concentration (valdecoxib)	0.5h	1.6h
Area under the plasma concentration-time curve (valdecoxib)	2.62 mg/L • h	2.73 mg/L • h
Elimination half-life of valdecoxib and parecoxib (healthy volunteers)	7.88; 0.69h (50mg)	NR; 0.25-0.58h (1 to 40mg)
Adverse events		
Most frequent after gynaecological surgery	Nausea, abdominal pain, headache, abdominal fullness, dizziness, vomiting, abnormal breath sounds and pruritus	



Parecoxib

Moderate to severe acute pain may be managed using opioids, local anaesthetics and nonsteroidal anti-inflammatory drugs (NSAIDs).[1] NSAIDs inhibit cyclo-oxygenase (COX) enzymes, which are involved in the synthesis of prostaglandins.[2] Nonselective NSAIDs block both COX-1 and COX-2.[2] COX-1, the constitutively expressed isoform of the enzyme, plays a key role in prostaglandin synthesis in the gastric mucosa, platelets and kidneys; it appears that the inhibition of this enzyme is associated with gastrointestinal and antiplatelet adverse events.[3] In contrast, inhibition of the inducible isoform COX-2 is thought to be primarily responsible for the anti-inflammatory and analgesic effects of NSAIDs.[4,5]

The development of COX-2-selective oral NSAIDs (e.g. celecoxib and rofecoxib) has resulted in drugs that provide effective relief of mild to moderate pain without gastrointestinal and antiplatelet adverse effects.[2] However, in cases of postoperative nausea and vomiting or where the oral route of administration is inaccessible after surgery, the use of orally administered NSAIDs may not be appropriate.[1] Currently, there are very few parenterally administered NSAIDs.[2] One exception is ketorolac, which has analgesic efficacy in the treatment of moderate to severe acute pain but is associated with gastrointestinal ulceration, renal function impairment and a predisposition to increased perioperative bleeding.[6] Ketorolac is contraindicated preoperatively.[7]

Parecoxib (parecoxib sodium), the focus of this profile, is a COX-2 specific inhibitor which can be administered as an intravenous or intramuscular injection. This prodrug of valdecoxib is in late phase clinical trials for the management (prevention and treatment) of acute pain, including moderate to severe postsurgical pain.[2]

1. Pharmacodynamic Profile

• Parecoxib is a water-soluble prodrug that undergoes complete and rapid biotransformation to valdecoxib – a potent and selective inhibitor of COX-2.[8] The dose of valdecoxib required to inhibit enzymatic activity by 50% was 0.005 μmol/L against the recombinant human COX-2 isoform compared with 140 μmol/L against the COX-1 isoform.[8]

Analgesic Effects

• The analgesic efficacy of parecoxib has been demonstrated in patients with postoperative pain following third molar extraction,[9-11] or gynaecological[12-14] or orthopaedic surgery;[15,16] these data are presented in section 3. The analgesic activity of intravenous parecoxib is also evident in a rat model of carrageenan-induced acute inflammation and pain.[8] In this model, intravenous parecoxib 30 mg/kg had a rapid onset of action, producing a complete blockade of hyperalgesia within 1 hour of administration. A dose of 5 mg/kg was required to produce analgesic effects in 50% of animals in this model. Parecoxib 30 mg/kg demonstrated similar activity to the same dose of ketorolac.[8]

Gastrointestinal Effects

• Healthy elderly volunteers (aged 65 to 75 years) were significantly less likely to develop gastrointestinal ulcers with parecoxib (n = 31) than with ketorolac (n = 31) in a double-blind, randomised trial (0 *vs* 23%, $p < 0.05$) [fig. 1].[17] The incidence of lesions (both erosions and ulcers) was also significantly lower for parecoxib recipients (fig. 1). Endoscopic evaluation indicated that there were no significant differences in gastrointestinal effects between parecoxib and placebo (n = 32). Parecoxib 40mg and placebo were administered intravenously twice daily for 7 days and ketorolac 15mg

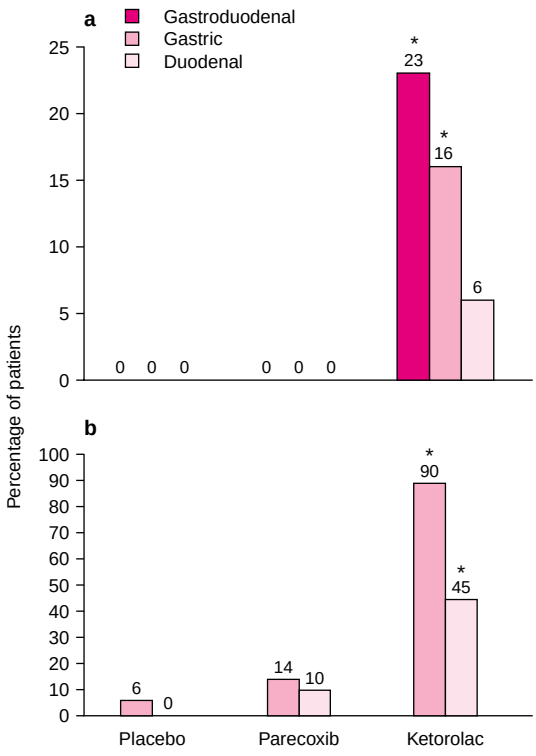


Fig. 1. Incidence of gastrointestinal ulcers (**a**) and lesions [both erosion and ulcers (**b**)] with parecoxib, ketorolac or placebo in 94 healthy elderly volunteers (aged 65 to 75 years) in a randomised, double-blind endoscopic study.[17] Parecoxib 40mg (n = 31) or placebo (n = 32) were given intravenously twice daily for 7 days and ketorolac 15mg (n = 31) was administered intravenously 4 times a day for 5 days following 2 days of placebo. Ulcers were defined as a break in the mucosa ≥3mm in diameter with unequivocal depth, and erosion was defined as a break in the mucosa without depth.[18] * $p < 0.05$ *vs* parecoxib and placebo.

was given intravenously 4 times a day for 5 days following 2 days of placebo (data were presented in an abstract).[17]

Effects on Platelet Function

• Platelet aggregation in response to arachidonate, ADP or collagen was not significantly altered from baseline with parecoxib 40mg twice daily for 3 days plus a single dose on day 4; similar results were observed with placebo in this randomised, double-blind, parallel-group trial in 20 healthy volunteers (data were presented in an abstract).[19]

Potential Drug Interactions

• Compared with placebo, parecoxib (40mg twice daily for 3 days followed by a single dose on day 4) did not significantly affect the anti-platelet effect of aspirin in response to various aggregants at most time-points; platelet aggregation with aspirin was lowered in response to arachidonate, ADP or collagen in a well controlled trial.[19] Aspirin 325mg was given as a single dose 2 hours after the final dose of either parecoxib or placebo.

• Platelet counts and prothrombin time were similar with coadministration of parecoxib and heparin to those recorded following heparin infusion alone in healthy volunteers in a nonblind nonrandomised trial (presented in an abstract).[20] 23 healthy volunteers received a bolus injection of heparin 4000U, which was followed by an infusion of heparin (initial dose 10 to 14 U/kg) for at least 36 hours. The heparin dose was adjusted to achieve partial thromboplastin time of 1.5 to 3.0 × baseline value. After a 2-day washout period, 18 healthy volunteers were treated with intravenous parecoxib 40mg twice daily for 6 days. A bolus injection of heparin (4000U) was given on day 5 followed by a 36-hour stable infusion at the rate determined above.[20]

2. Pharmacokinetic Profile

Data in this section are from studies in healthy volunteers[21-23] or patients with postoperative dental pain[10,24,25] and were obtained from abstracts[22-24,26] or posters.[10,21,25]

• The maximum plasma concentrations (C_{max}) of valdecoxib were 25 and 30% greater after intravenous than intramuscular administration of parecoxib 20 or 40mg in patients with moderate to severe postoperative dental pain in a randomised, double-blind, placebo-controlled trial; time to C_{max} (t_{max}) was approximately 0.5 hours after intravenous administration and 1.5 hours after intramuscular administration.[24] However, the total ex-

posure to valdecoxib [area under the plasma concentration-time curve (AUC_{24h})] was independent of the route of administration. Values for AUC_{24h} and C_{max} were not presented.[24]

Intravenously Administered Parecoxib

- Parecoxib was rapidly converted after intravenous administration of 50mg in 12 healthy volunteers; $t_{½}$ was 0.69 hours.[21] C_{max} of valdecoxib with a single intravenous dose of parecoxib 50mg was 1.02 mg/L achieved 0.6 hours after administration of the prodrug. With multiple doses (50mg daily or twice daily), C_{max} of valdecoxib was 1.40 mg/L (day 10); steady-state plasma concentrations were reached on day 7. AUC_{∞} of valdecoxib with a single intravenous dose of parecoxib was 7.80 mg/L · h; with multiple doses, AUC_{12h} was 8.16 mg/L · h (day 10). Valdecoxib had a $t_{½}$ of 7.88 hours and was the primary compound recovered in the urine within 48 hours of administration of parecoxib.[21]

- Mean AUC_{24} and mean C_{max} of valdecoxib increased dose-proportionately with parecoxib 1 to 100mg given as a single intravenous dose in 356 patients after dental surgery (AUC_{24} 0.15 to 13.61 mg/L · h; C_{max}, 0.026 to 2.16 mg/L).[10] With the 20mg dose, mean AUC_{24h} and C_{max} were 2.62 mg/L · h and 0.45 mg/L. Values for t_{max} were consistent (0.5 to 0.9 hours) across all parecoxib doses.[10]

Intramuscularly Administered Parecoxib

- Parecoxib (1 to 40mg) was rapidly converted after administration of a single intramuscular dose in 56 healthy volunteers; $t_{½}$ of parecoxib ranged between 0.25 and 0.58 hours.[22] C_{max} of valdecoxib was reached 1.1 to 3.5 hours after administration of the prodrug.[22] C_{max} and AUC_{∞} of valdecoxib increased dose-proportionately with increasing doses of parecoxib. Values for C_{max} and AUC_{∞} were not provided.[22]

- Dose proportional increases in mean C_{max} (0.027 to 0.39 mg/L) and mean AUC_{24h} (0.14 to 2.73 mg/L · h) of valdecoxib were also observed with parecoxib (1 to 20mg) administered as a single intramuscular dose to 353 patients with postoperative dental pain.[25] Median t_{max} was 1.6 hours. The change in plasma concentrations of valdecoxib correlated with the onset and duration of analgesia.[25]

Potential Drug Interactions

- Parecoxib is rapidly hydrolysed by the liver to valdecoxib, which is a substrate for the cytochrome P450 (CYP) isoenzymes 3A4 and 2C9. To examine potential drug interactions with agents metabolised by CYP3A4, midazolam 0.07 mg/kg (an accepted probe for CYP3A4 drug interactions) was administered as an intravenous infusion over 5 minutes to 12 healthy volunteers 1 hour after intravenous parecoxib (40mg) or placebo in a randomised, double-blind, crossover trial.[23] The plasma disposition curves of midazolam were similar for volunteers pretreated with parecoxib and those receiving placebo. In addition, C_{max}, systemic clearance and $t_{½}$ for midazolam did not differ significantly for parecoxib- versus placebo-pretreated volunteers. Quantitative data were not reported.[23]

- Compared with placebo, intravenous parecoxib 40mg did not significantly affect the plasma disposition curve, C_{max}, systemic clearance or $t_{½}$ of intravenous propofol 2 mg/kg administered to 12 healthy volunteers in a randomised, double-blind, crossover trial.[26]

3. Therapeutic Trials

The efficacy of parecoxib (1 to 100mg) in the treatment of acute postoperative pain after third molar extraction,[9-11] gynaecological surgery[12-14] or orthopaedic surgery[15,16] has been evaluated in several clinical trials. Trials were of randomised, double-blind, parallel-group and placebo-controlled design, and involved 57 to 457 patients. Most trials[9-12,14,16] had an active comparator (intravenous morphine 4mg and/or intravenous ketorolac 30mg or intramuscular ketorolac 30 or 60mg). Parecoxib was given as a single intravenous or in-

tramuscular dose. All data were presented in abstracts[13-16] or posters.[9,11,12,25]

Primary measures for most trials included pain intensity difference (categorical scale) [PID], pain relief (PR), time to rescue medication and time to onset of analgesia. Other efficacy measures included weighted total pain relief (TOTPAR),[11] weighted summed PID (SPID),[11] patient global evaluation,[9,12,15] visual analogue scale (VAS) pain scores[13] and cumulative amount of morphine used at 24 hours post-treatment with parecoxib or placebo.[15]

Intravenous or Intramuscular Administration Following Dental Surgery

• Intravenous or intramuscular parecoxib (20 or 40mg) demonstrated greater analgesic efficacy (measured by PID and PR) than placebo and similar analgesic efficacy to intramuscular ketorolac (60mg) through 24 hours in patients with postoperative dental pain (n = 304; p-values were not reported).[9] At 4 hours, mean scores for PID were 0 for placebo, ≈1.15 and ≈1.3 for intravenous and intramuscular parecoxib 20mg, ≈1.45 and ≈1.65 for intravenous and intramuscular parecoxib 40mg, and ≈1.85 for ketorolac 60mg; mean PR scores were ≈0.5, ≈2.2, ≈2.3, ≈2.6, ≈2.8 and 3 for placebo, intravenous and intramuscular parecoxib 20mg, intravenous and intramuscular parecoxib 40mg and ketorolac, respectively. All values were estimated from graphs.[9]

• Median time to onset of analgesia in this trial was 12 or 13 minutes for all active treatments; these times were significantly shorter than that for placebo (>24 hours).[9] The median time to rescue medication for the 20mg intravenous or intramuscular dose of parecoxib was similar to that for intramuscular ketorolac 60mg but shorter than that for intravenous or intramuscular parecoxib 40mg (p-values were not reported) [fig. 2].[9]

• Approximately 65% (20mg dose) and 90% (40mg dose) of patients receiving intravenous or intramuscular parecoxib rated their medication as good or excellent compared with ≈75% of patients receiving intramuscular ketorolac (patient global evaluation).[9] In contrast, 0 and 8% of placebo recipients rated their medication as excellent and good, respectively.

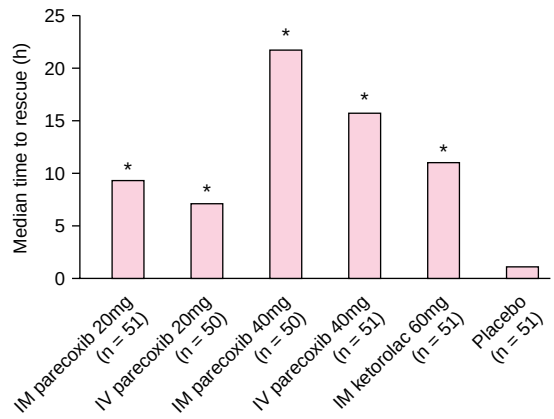


Fig. 2. Median time to rescue medication for 304 patients with postoperative dental pain treated with a single dose of intravenous (IV) or intramuscular (IM) parecoxib 20 or 40mg, IM ketorolac 60mg or placebo in a randomised, double-blind, parallel-group trial.[9] * $p < 0.05$ *vs* placebo.

• Intramuscular parecoxib 20mg was more effective than placebo and lower doses of parecoxib (1, 2, 5 and 10mg) at reducing pain intensity (SPID) and providing pain relief (TOTPAR) in 353 patients with postoperative pain following dental surgery.[11] 24-hour SPID and TOTPAR scores, respectively, were 21 and 47 for parecoxib 20mg, compared with ≈3.5 to ≈8 and ≈19 to ≈21 for parecoxib 1 to 10mg and –1 and ≈13 for placebo. Data were estimated from graphs.[11] PR for parecoxib 20mg was similar to that for intramuscular ketorolac 30mg for the first 12 hours after administration and significantly greater than that for ketorolac 30mg from 12 to 24 hours (p-values were not reported).[11] Median time to onset of analgesia was 14 minutes for both parecoxib 20mg and ketorolac 30mg; time to rescue medication was 7.7 and ≈8 hours, respectively.

• Doses of intravenous parecoxib ≥5mg provided greater analgesic effect (measured using PID and PR) than placebo over 24 hours in 457 patients with postoperative dental pain (p-values were not reported).[10] The 20, 50 and 100mg doses of parecoxib had similar analgesic efficacy to that of intravenous ketorolac 30mg.[10] Median time to onset of analgesic activity was 9 to 11 minutes for intravenous parecoxib 20 to 100mg and 12 minutes for intravenous ketorolac 30mg. Time to rescue medication for parecoxib 20, 50 and 100mg was 8, 10.5 and 13.5 hours compared with 7.9 hours for ketorolac 30mg.[10]

Intravenous Administration Following Gynaecological Surgery

• Intravenous parecoxib (20 or 40mg) was significantly more effective than placebo (p-values were not reported) and as effective as intravenous ketorolac (30mg) at reducing pain intensity (PID) and providing pain relief (PR) following abdominal hysterectomy or myomectomy in 202 women.[12] The extent and duration of analgesic effect after both doses of parecoxib was significantly better than that for intravenous morphine (4mg) from 1.5 to at least 8 hours after treatment (p-values were not reported). Values for PID were 1.25 and 1.4 for parecoxib 20 and 40mg compared with ≈1.4 for ketorolac 30mg, 1.1 for morphine 4mg and 0.8 for placebo (values were estimated from a graph). Parecoxib 20mg provided comparable efficacy to the 40mg dose across all variables measured (including PID, PR and TOTPAR).

• Median time to analgesia was similar among all active treatments (range 10 to 23 minutes). Median time to rescue medication was 6.2, 6.5 and 6 hours for parecoxib 20 and 40mg and ketorolac 30mg, respectively, which was significantly longer than times for intravenous morphine 4mg (2.6 hours) and placebo (1.8 hours) [p-values were not reported].[12] 78, 73, 61, 44 and 16% of patients receiving ketorolac, parecoxib 20mg, parecoxib 40mg, intravenous morphine 4mg and placebo, respectively, rated their medication as good or excellent.[12]

• Parecoxib 40mg was as effective as ketorolac 30mg and intravenous morphine 4mg and significantly more effective than placebo at reducing pain intensity at 45, 60 and 90 minutes after administration in 72 female patients who had undergone gynaecological surgery the previous day.[14] The analgesic effect of the 20mg dose of parecoxib did not differ significantly from that of placebo at any time-point (15, 30, 45, 60, 90 or 120 minutes) after administration. Time to remedication after parecoxib 40mg (8 hours) was similar to that after ketorolac 30mg (7.8 hours) but was significantly longer than that after parecoxib 20mg, morphine 4mg and placebo (6.2, 5 and 3.4 hours, respectively, all $p < 0.05$).[14]

• Parecoxib 20 and 40mg significantly decreased the patient-controlled morphine requirements at 12 (29 and 32%, $p < 0.05$) and 24 hours (33 and 35%, $p < 0.05$) compared with placebo in 57 female patients following major gynaecological surgery.[13] There were no differences between the 2 doses of parecoxib for this parameter. There were no significant differences among the 3 treatment groups in VAS pain scores at 12 (1.4 to 1.7) or 24 (1.1 to 1.2) hours.[13]

Intravenous Administration Following Orthopaedic Surgery

• Intravenous parecoxib 40mg was as effective as intravenous ketorolac 30mg and significantly more effective than intravenous morphine 4mg at reducing PID and PR in 208 patients following knee replacement orthopaedic surgery (p-values were not reported).[16] Median time to onset of analgesia and median time to rescue medication were similar after parecoxib 40mg (11 minutes and 5.17 hours, respectively) to those after ketorolac 30mg (12 minutes and 4.58 hours). In contrast, median time to onset of analgesia was significantly shorter and median time to rescue medication was significantly longer with parecoxib than with intravenous morphine 4mg (15 minutes and 2.12 hours) or placebo (31 minutes and 1.8 hours) [p-values were not reported].[16]

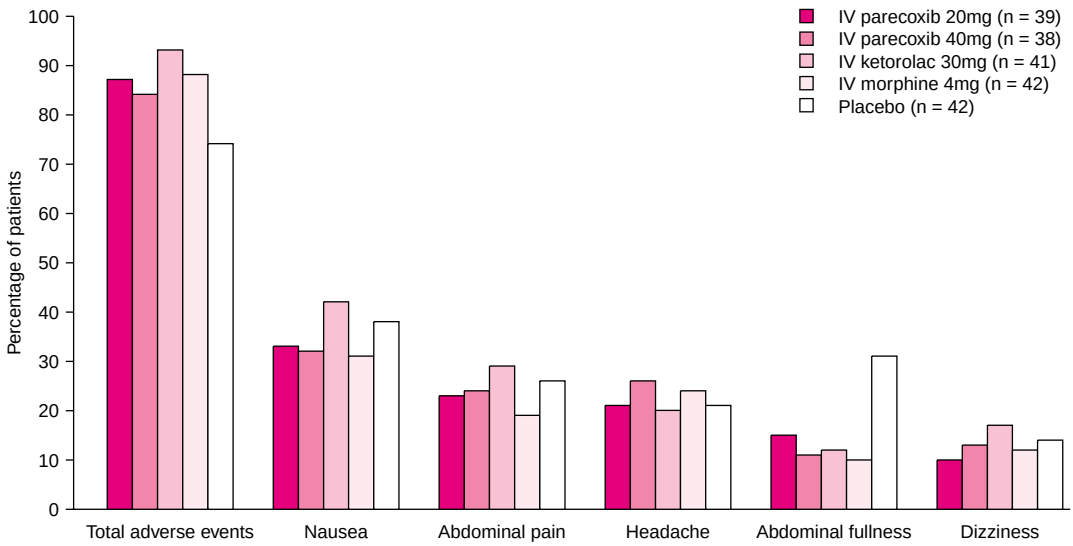


Fig. 3. Incidence of adverse events (%) after a single dose of intravenous (IV) parecoxib 20 or 40mg, IV ketorolac 30mg, IV morphine 4mg or placebo in 202 female patients with moderate to severe pain following abdominal hysterectomy or myomectomy in a multicentre, double-blind, randomised trial.[12]

• Following total hip arthroplasty, patients treated with intravenous parecoxib 20mg (n = 60) or 40mg (n = 53) used significantly less morphine at 24 and 36 hours than those treated with placebo (n = 62); the mean amount of morphine used at 24 hours after the dose was 44 and 36mg for parecoxib (20 or 40mg) recipients versus 58mg for placebo recipients ($p = 0.01$ and $p < 0.001$ *vs* placebo).[15]

• In addition, patient global evaluation scores were significantly higher at 24 and 36 hours and PID scores were significantly higher at most (20mg) or all (40mg) assessment points for parecoxib than placebo (p-values were not reported).[15]

4. Tolerability

All data presented in this section are from preliminary presentations (abstracts or posters) of the randomised, controlled, double-blind, parallel-group trials discussed in section 3.

Postdental Surgery: Intravenous or Intramuscular Administration

• Intravenous (1 to 100mg) or intramuscular (1 to 40mg) parecoxib was well tolerated in trials involving 304 to 457 patients with postoperative dental pain; ketorolac, the comparator drug, was administered as a 30 or 60mg intramuscular dose or 30mg intravenous dose.[9-11]

• The incidence of adverse events was similar across treatment groups; adverse events which occurred with an incidence of ≥5% irrespective of treatment agent in all 3 trials included nausea, alveolar osteitis, dizziness and headache (quantitative data were not reported).[9-11] In addition, vomiting, injection site ecchymosis or reaction, abdominal pain, pharyngitis and vein pain were reported by ≥5% of patients in any treatment group in at least 1 trial (percentages were not reported).[10,11] There were no clinically significant laboratory results.[10,11]

Postgynaecological Surgery: Intravenous Administration

• Adverse events with intravenously administered parecoxib (20 or 40mg) compared with intravenous ketorolac (30mg), intravenous morphine (4mg) or placebo in 202 female patients with moderate to severe pain following abdominal hysterectomy or myomectomy are presented in figure 3.[12] The most common adverse events occurring in ≥10% of patients irrespective of treatment included nausea, abdominal pain, headache, abdominal fullness, dizziness, back pain, fever, hypoactive bowel sounds, vomiting, tachycardia, somnolence, abnormal breath sounds and pruritus. Most adverse events were mild or moderate in severity. Statistical significance was not reported.[12]

• Emesis was reported by 67, 65 and 56% of patients and itching was experienced by 22, 18 and 28% of patients (n = 57) receiving intravenous parecoxib 20 or 40mg or placebo, respectively, after major gynaecological surgery in a double-blind trial.[13] No other adverse events were reported by investigators.[13]

• There were no parecoxib-related adverse effects after intravenous doses of 20 or 40mg in a randomised, double-blind trial involving 72 female patients with pain following gynaecological surgery.[14]

Postorthopaedic Surgery: Intravenous Administration

• Intravenous parecoxib 20 or 40mg was well tolerated in patients following knee replacement surgery (n = 208)[16] or total hip arthroplasty (n = 175).[15] The incidence of adverse events with parecoxib (20 or 40mg) was generally similar to that with placebo after hip arthroplasty, although significantly fewer patients using parecoxib 40mg reported fever (p = 0.003) and/or vomiting (p = 0.05).[15]

5. Parecoxib: Current Status

Parecoxib, an injectable COX-2 specific inhibitor, is in late-phase clinical trials for the management (the prevention and treatment) of acute pain, including moderate to severe postsurgical pain. The agent effectively relieves pain compared with placebo and intravenous morphine 4mg and shows analgesic efficacy similar to that of the NSAID ketorolac in patients who have undergone dental, gynaecological or orthopaedic surgery. Parecoxib is well tolerated and, unlike ketorolac, is not associated with an increased risk of gastrointestinal ulcers.

References

1. Carr DB, Goudas LC. Acute pain. Lancet 1999 Jun 12; 353: 2051-8
2. Jain KK. Evaluation of intravenous parecoxib for the relief of acute post-surgical pain. Expert Opin Invest Drug 2000; 9 (11): 2717-23
3. Fosslien E. Adverse effects of nonsteroidal anti-inflannatory drugs on the gastrointestinal system. Ann Clin Lab Sci 1998; 28 (2): 67-81
4. Bolten WW. Scientific rationale for specific inhibition of COX-2. J Rheumatol 1998 May 25; 25 Suppl. 51: 2-7
5. Needleman P, Isakson PC. The discovery and function of COX-2. J Rheumatol 1997; 24 Suppl. 49: 6-8
6. McArdle P. Intravenous analgesia. Crit Care Clin 1999 Jan; 15: 89-104
7. Mosby. Mosby's GenRx Update 3. Ketorolac Tromethamine 2001
8. Talley JJ, Bertenshaw SR, Brown DL, et al. *N*-[[(5-Methyl-3-phenylisoxazol-4-yl)-phenyl]sulfonyl]propanamide, sodium salt, parecoxib sodium: a potent and selective inhibitor of COX-2 for parenteral administration. J Med Chem 2000 May 4; 43: 1661-3
9. Hubbard RC, Kuss ME, Daniels SE, et al. Parecoxib, a new parenteral COX-2 specific inhibitor with an enhanced analgesic profile. WWPC; 2000 Jul; San Francisco, CA
10. Daniels SE, Kuss M, Mehlisch DR, et al. Pharmacokinetic and efficacy evaluation of intravenous parecoxib in a postsurgical dental pain model [poster]. ASCPT; 2000 Mar; Los Angeles (CA)
11. Mehlisch D, Kuss M, Bauman A, et al. Onset and duration of analgesia of intramuscular doses of paracoxib, and ne parenteral COX-2 inhibitor, in postoperative dental pain [poster]. APS; 1999 Nov; Ft Lauderdale (FL)
12. Langland F, Turpin M, Waller P, et al. A comparative analgesic efficacy study of parecoxib, a new COX-2 specific inhibitor, in post-gynecological surgery patients [poster no. 814]. Presented at the 19th Annual Scientific Meeting of the American Pain Society; 2000 Nov
13. Tang J, Chen X, White PF, et al. Effect of parecoxib, a new cyclooxygenase-2 inhibitor, on the postoperative analgesia [abstract no. S270]. Anesth Analg 2001; 92 Suppl.: 2
14. Kenaan CA, Bikhazi GB, Deepika K, et al. Analgesic activity and safety of parecoxib in post-surgical patients: an interim report [abstract no. 257]. Anesth Analg 2001; 92 Suppl.: S257
15. Malan TP, Marsh G, Grossman E, et al. Evaluation of the opiod-sparing effectiveness of parecoxib sodium, a new COX-2 specific inhibitor, in the management of postoperative pain following total hip arthroplasty [abstract no. 774]. J Pain Symptom Manage 2001 Apr; 2 Suppl. 1: 38
16. Rasmussen GL, Stecker K, Hogue CW, et al. A comparative analgesic efficacy study of parecoxib sodium, a new inject-

able COX-2 inhibitor, in post-orthopedic surgery patients [abstract no. 776]. J Pain Symptom Manage 2001; 2 Suppl. 1: 39
17. Hubbard RC, Kuss ME, LeComte DL, et al. An endoscopic study of the gastroduodenal effects of SC-69124A, a parenteral COX-2-specific inhibitor, in the elderly [abstract]. Gastroenterology 2000 Apr; 118 Suppl. 2 (Pt 2): 250
18. Hubbard ME, Kuss D, LeComte S, et al. An endoscopic study of the gastroduodenal effects of parecoxib sodium, an injectable COX-2 inhibitor in the elderly. Dig Dis Week; 2000 May 21-24; San Diego (CA)
19. Noveck RJ, Kuss ME, Qian J, et al. Parecoxib sodium, an injectable COX-2 specific inhibitor, does not affect aspirin-mediated platelet function [abstract no. 19]. Regional Anesthesia and Pain Medicine 2001 Mar-Apr; 26 (2 Suppl.): ASRA 26th Annual Meeting: 2001 May 10-13: Vancouver; W.B Saunders Company, 2001: 19
20. Noveck RJ, Kuss ME, Qian J, et al. Parecoxib sodium, an injectable COX-2 specific inhibitor, does not affect heparin-regulated blood coagulation parameters [abstract no. 20]. Regional Anesthesia and Pain Medicine 2001 Mar-Apr; 26 (2 Suppl.): ASRA 26th Annual Meeting: 2001 May 10-13; Vancouver; W.B. Saunders Company, 2001: 20
21. Grossman E, Hubbard R, Laurent A, et al. A safety and pharmacokinetic study of analgesic doses of parecoxib sodium, a new COX-2 specific inhibitor, in healthy subjects [poster no. 653]. Presented at the 19th Annual Scientific Meeting of the American Pain Society; 2000 Nov
22. Karim A, Laurent A, Kuss M, et al. Single dose tolerability and pharmacokinetics of parecoxib sodium, a COX-2 specific inhibitor, following intravenous administration [abstract no. A-944]. Annual Meeting of the American Society of Anesthesiologists, 2000
23. Ibrahim A, Karim A, Feldman J, et al. Effects of parecoxib, a parenteral COX-2 specific inhibitor, on the disposition of midazolam [abstract no. 529]. Annual Meeting of the American Society of Anesthesiologists, 2000
24. Hubbard R, Kuss M, Talwalker S, et al. Evaluation of parecoxib, a new injectable cyclooxygenase-2-specific inhibitor, for the treatment of pain [abstract no. 266]. Ann Emerg Med 2000 Oct; 36 Suppl.: S69
25. Mehlisch D, Kuss M, Bauman A, et al. Correlation of pharmacokinetics (PK) with onset and duration of analgesia of intramuscular doses of parecoxib, in postoperative dental pain [poster no. PIII-7]. ASCPT; 2000 Mar; Los Angeles (CA)
26. Ibrahim A, Park S, Feldman J, et al. Effects of parecoxib, a parenteral COX-2 specific inhibitor, on the disposition of propofol [abstract no. 530]. Anesthesiology 2000 Sep; 93 (3A Suppl.): 56

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