

Effects of Parecoxib, a Parenteral COX-2-specific Inhibitor, on the Pharmacokinetics and Pharmacodynamics of Propofol

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Background: Parecoxib, a cyclooxygenase-2-specific inhibitor with intended perioperative analgesic and antiinflammatory use, is a parenterally administered inactive prodrug undergoing rapid hydrolysis *in vivo* to the active cyclooxygenase-2 inhibitor valdecoxib. Both parecoxib and valdecoxib inhibit human cytochrome P450 2C9 (CYP2C9) activity *in vitro*. Thus, a potential exists for *in vivo* interactions with other CYP2C9 substrates, including propofol. This investigation determined the influence of parecoxib on the pharmacokinetics and pharmacodynamics of bolus dose propofol in human volunteers.

Methods: This was a randomized, balanced crossover, placebo-controlled, double-blind, clinical investigation. Twelve healthy 21- to 37-yr-old subjects were studied after providing institutional review board–approved written informed consent. Each subject received a 2-mg/kg intravenous propofol bolus 1 h after placebo (control) or 40 mg intravenous parecoxib on two occasions. Venous concentrations of propofol, parecoxib, and parecoxib metabolites were determined by mass spectrometry. Pharmacokinetic parameters were determined by noncompartmental analysis. Pharmacodynamic measurements included clinical endpoints, cognitive function (memory, Digit-Symbol Substitution Tests), subjective self-assessment of recovery (Visual Analog Scale) performed at baseline, 15, 30, 60 min after propofol, and sedation depth measured by Bispectral Index.

Results: Propofol plasma concentrations were similar between placebo- and parecoxib-treated subjects. No significant differences were found in pharmacokinetic parameters (C_{max}, clearance, elimination half-life, volume of distribution) or pharmacodynamic parameters (clinical endpoints [times to: loss of consciousness, apnea, return of response to voice], Bispectral Index scores, Digit-Symbol Substitution Test scores, memory, Visual Analog Scale scores, propofol EC₅₀).

Conclusions: Single-bolus parecoxib, in doses to be used perioperatively, does not alter the disposition or the magnitude or time course of clinical effects of bolus propofol. Effects on a propofol infusion were not evaluated.

PARECOXIB is a highly selective nonsteroidal cyclooxygenase-2 (COX-2) inhibitor undergoing clinical develop-

ment, with intended use perioperatively as an analgesic agent.^{1,2} Parecoxib may be administered preoperatively or postoperatively for its analgesic and antiinflammatory effects. Both parenteral parecoxib and oral valdecoxib have shown efficacy in pain relief that is similar to the currently available parenteral nonselective cyclooxygenase inhibitor, ketorolac, and superior to placebo.^{3–5} Moreover, parecoxib has significantly fewer side effects (gastrointestinal, platelet aggregation) than ketorolac.¹

Parecoxib is a parenterally administered inactive prodrug that undergoes rapid amide hydrolysis *in vivo* to the pharmacologically active COX-2 inhibitor, valdecoxib (fig. 1).² Valdecoxib is metabolized primarily to 1-hydroxyvaldecoxib, catalyzed by hepatic cytochrome P450s (CYP) 2C9 and 3A4.⁶ Because valdecoxib is a substrate for hepatic CYPs 2C9 and 3A4 and both parecoxib and valdecoxib are inhibitors of CYP2C9, there is a potential for parecoxib and valdecoxib interactions with other similarly metabolized drugs. The only commonly used anesthetic that undergoes significant metabolism by CYP2C9 is propofol.⁷ The first aim of this investigation was to determine the effect of parecoxib on the pharmacokinetics (systemic clearance) of propofol, and the second aim was to determine the effect of parecoxib on the pharmacodynamics (hypnotic effects, hemodynamic response, and recovery profile) of propofol.

Methods

Participants

Twelve healthy subjects (six men and six women; age, 29 ± 5 yr) within 30% of normal body weight (75 ± 13 kg) were studied after providing institutional review board–approved written informed consent (University of Washington, Seattle, WA). Individuals were excluded if they were pregnant, were taking benzodiazepines, barbiturates, opioids, nonsteroidal antiinflammatory drugs (NSAIDs), or drugs known to cause induction or inhibition of hepatic enzymes, or were at risk for aspiration. Subjects fasted for a minimum of 6 h before initiation of study. Sample size was determined using calculations based on interindividual variability in propofol clearance because intraindividual variability was unknown. Power analysis using published propofol clearances suggested that a 25% difference in propofol clearance between placebo and parecoxib could be detected with 80% power using 12 subjects, assuming an estimated SD for the difference of 0.11.

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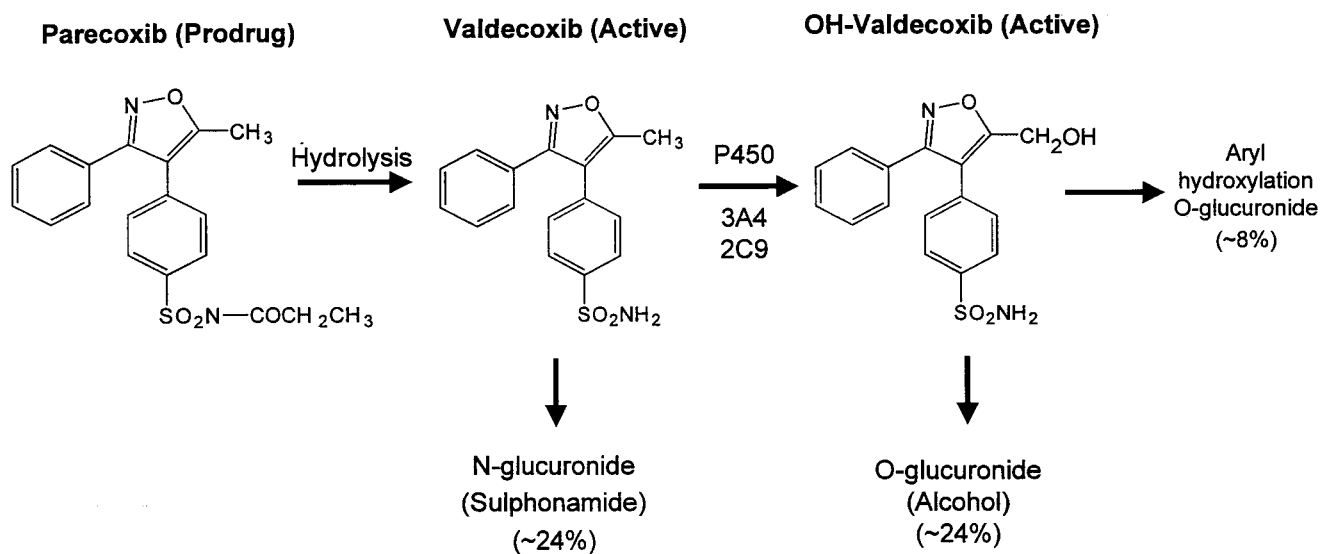


Fig. 1. Major metabolic pathways of parecoxib in humans *in vivo*.

Study Design

This was a randomized, balanced crossover, placebo-controlled, double-blind, clinical investigation. Each subject served as his or her own control and underwent physical and laboratory examination (hematology, biochemistry, urinalysis, hepatitis B surface antigen test, drug toxicology tests) both before the initiation and after the completion of the study.

Subjects received a propofol (2 mg/kg intravenous) bolus over 20 s on two occasions: 1 h after placebo (control) and 1 h after 40 mg intravenous parecoxib. This dose and timing of parecoxib administration was selected to mimic intended clinical use (typically an hour before anesthetic induction). The sequence was randomized, and the two sessions were separated by 7–14 days. Peripheral intravenous catheters were inserted in separate arms for drug administration and blood sampling. Supplemental oxygen and monitoring (electrocardiography, blood pressure, pulse oximetry) were provided for all subjects. An investigator administered propofol and, if necessary, provided bag and mask ventilation while subjects were unconscious or apneic. A trained independent observer, who was blinded to the purpose of the investigation and the identity of the drug pretreatment, was present throughout the study period to record hemodynamic and other effect data and to administer the psychomotor tests. Venous blood samples were obtained at baseline and 1, 3, 5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420, 480, 540, and 600 min after propofol administration. Samples were centrifuged and plasma was removed and stored at -20°C until analysis.

Analytical Methods

Plasma propofol concentrations were determined by gas chromatography-mass spectrometry (Hewlett-Pack-

ard 5890 II-5972A MSD, Wilmington, DE) using a fully validated assay conducted according to Good Laboratory Practice. Plasma (200 μl), 50 μl sodium hydroxide (1 M), and 600 μl ethyl acetate-heptane (1:1) containing the internal standard thymol (150 ng) were vortexed in a microcentrifuge tube and centrifuged (3 min at 1,400g), and the upper organic layer was transferred to an autosampler vial for analysis. After samples were introduced onto a 30 m \times 0.32 mm \times 0.25 μm DB-5 column (J & W, Folsom, CA) by splitless injection, chromatography was at a constant flow of 3 psi helium carrier gas. Oven temperature was 50°C for 1 min and then increased to 120°C at $25^{\circ}\text{C}/\text{min}$, to 180°C at $10^{\circ}\text{C}/\text{min}$, and to 300° at $30^{\circ}\text{C}/\text{min}$ and was then held for 1 min. The injector and transfer line temperatures were 240 and 300°C , respectively. Detection (electron impact) was with selected ion monitoring of propofol (m/z 163.1) and thymol (m/z 135.1). Propofol was quantified from integrated peak area ratios using calibration standards in plasma (0.02–5.0 $\mu\text{g}/\text{ml}$). Coefficients of variation were 8, 5, and 4% for interday and 6, 5, and 4% intraday quality control samples at 0.02, 0.5, and 4 $\mu\text{g}/\text{ml}$. Accuracy and recovery were greater than 89% at all concentrations. The linear range was 0.02–5 $\mu\text{g}/\text{ml}$ ($r^2 > 0.97$), and the limit of quantitation was defined as the lowest point on the standard curve.

Plasma concentrations of parecoxib, valdecoxib, and 1-hydroxyvaldecoxib were determined by high-pressure liquid chromatography with tandem mass spectrometry using a validated assay conducted according to Good Laboratory Practice. After adding the $^{13}\text{C}_6$ respective internal standards, plasma was extracted using a C8 solid-phase extraction column. Analytes (> 98% recovery) were separated by reversed-phase liquid chromatography on a C18 column, detected by multiple reaction monitoring, and were quantified using standard curves

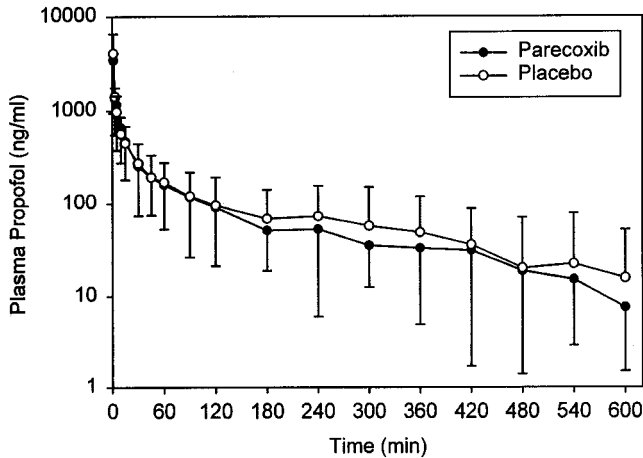


Fig. 2. Propofol plasma concentrations after parecoxib compared with placebo (mean \pm SD, $n = 12$). The propofol Cp_{50} for loss of consciousness (*i.e.*, plasma concentration at which 50% of subjects are unresponsive to voice) is 2.3–2.7 $\mu\text{g/ml}$.^{25–27}

of peak area ratios (*vs.* respective internal standards). Assay ranges were 0.5–200 ng/ml for valdecoxib and 1-hydroxyvaldecoxib and 5–2,000 ng/ml for parecoxib. Coefficients of variation for valdecoxib, 1-hydroxyvaldecoxib, and parecoxib were 10, 9, and 3% (interday) and 14, 9, and 12% (intraday) at the limit of quantitation.

Clinical Effects

Times at which subjects reached predefined clinical endpoints were recorded. The endpoint for loss of consciousness was the time at which the subject dropped a syringe held between the thumb and index finger with the elbow at a 45° angle to the table, previously validated as an endpoint of the hypnotic effects of anesthetic agents.^{8,9} The following parameters were recorded by the blinded observer, beginning with administration of propofol: time to loss of response to voice command, time to loss of eyelash reflex, time to apnea, time to return of spontaneous ventilation (the first minute that the subject has resumed a stable respiratory pattern of a minimum of 6 breaths/min), time to eye opening, and time to return of response to voice command.

The speed of awakening and return of preoperative baseline cognitive function were assessed by Digit-Symbol Substitution Test (DSST)^{10,11} and a memory test. The DSST and memory test were given at baseline (before parecoxib–placebo), before propofol, and at 15, 30, and 60 min after propofol administration. The DSST score represents the number of correct substitutions completed in 90 s. For the memory test, each subject listened through headphones to a prerecorded tape of 16 nouns balanced on word frequency and normative free recall^{12–14} and were asked to recall immediately as many words as possible. A different list of nouns was presented each time the memory test was administered. The memory test was scored by the number of correct words recalled.

Subjective self-assessment of sedation, nausea, and anxiety was quantified by Visual Analog Scale (VAS). Attributes assessed (scored from 0 to 100) included level of alertness or sedation (almost asleep to wide awake), energy level (no energy to full of energy), confusion (confused to clear headed), clumsiness (extremely clumsy to well-coordinated), anxiety (calm and relaxed to extremely nervous), and nausea (no nausea to worst nausea). These three tests (VAS, memory, and DSST) were given at baseline (before drug administration) and repeated at 15, 30, and 60 min after propofol administration.

Bispectral Index

The electroencephalographic signal was acquired using the BIS sensor (Aspect Medical Systems, Natick, MA) electrodes applied to the forehead and temple using a frontal-temporal montage and the Bispectral Index (BIS monitor, model A1050, software version 3.0; Aspect Medical Systems). BIS values (with 30 s smoothing) were recorded every 5 s by an IBM-compatible computer connected by serial cable. Data were recorded using Hyperterm (Windows 95; Microsoft, Redmond, WA), and the values were displayed using Excel 97 (Microsoft). The

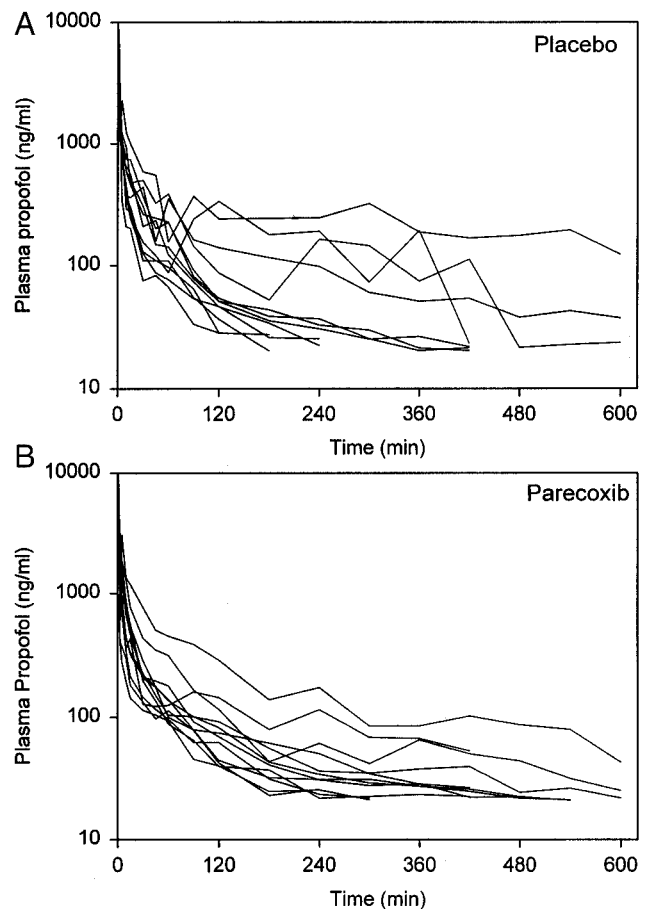


Fig. 3. Individual propofol concentrations *versus* time after placebo (A) and parecoxib (B).

Table 1. Propofol Pharmacokinetic Parameters

	Parecoxib + Propofol	Placebo + Propofol	P Value
AUC (0-∞) (ng · h · ml ⁻¹)	1,020 ± 543	1,183 ± 1,105	0.979
C _{max} (ng/ml)	3,515 ± 2,489	3,854 ± 2,504	0.734
CL (l/h)	185 ± 106	199 ± 119	0.979
VD _{ss} (l)	677 ± 345	448 ± 220	0.098
T _{max} (h)	0.02 ± 0.01	0.03 ± 0.03	0.443
K _{el} (h ⁻¹)	0.21 ± 0.11	0.34 ± 0.22	0.072
T _{1/2} (h)	4.37 ± 2.38	3.43 ± 2.70	0.444

Area under the curve (AUC), maximum observed plasma concentration (C_{max}), plasma clearance (CL), and distribution volume (VD_{ss}) were log-transformed before analysis of variance.

T_{max} = time to maximum plasma concentration; K_{el} = terminal elimination rate constant; T_{1/2} = terminal elimination half-life.

BIS monitor was applied before parecoxib-placebo administration. BIS scores at intervals corresponding to blood sampling times during emergence were compared with baselines before and after parecoxib-placebo administration for recovery of anesthetic effect.

Data Analysis

Propofol plasma concentration-time data for each subject were analyzed by noncompartmental and multicompartamental nonlinear regression analysis for determination of pharmacokinetic parameters using SAS, release 6.12 (SAS Institute Inc., Cary, NC). Terminal elimination half-life was estimated by linear regression of the log concentration-*versus*-time curve, systemic clearance was calculated as dose/area under the plasma time-concentration time curve (AUC), and steady-state volume of distribution (V_{dss}) was calculated as dose · AUMC/AUC². Parameters were compared between groups using Student's paired *t* test.

Analysis of variance (ANOVA) was performed on propofol AUC, maximum observed plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal elimination half-life (T_{1/2}), terminal elimination rate constant (K_{el}), plasma clearance (CL), and distribution volume (VD_{ss}). AUCs, C_{max}, CL, and VD_{ss} were natural log-transformed before ANOVA. In the ANOVA model, sources of variation included were sequence (1 or 2), subjects nested within sequence, period (1 or 2), and treatment (placebo *vs.* parecoxib). Effects due to subject were random, whereas all other effects were fixed. Sequence effect was tested by subject nested within sequence as the between-subject error term in the denominator of the F statistic. All other effects were tested by the within-subject mean square error from the ANOVA model. Within the ANOVA, pairwise comparison was performed to assess whether pretreatment with parecoxib had any effect on pharmacokinetics of propofol. Using the standard error estimate on the difference obtained from ANOVA, 90 and 95% confidence intervals for the difference between the two treatments were calculated. The differences and the lower and upper limits of the 90 and 95% confidence

intervals were exponentiated to obtain the ratios of mean and confidence interval in the original scale.

Pharmacodynamic data were analyzed according to an inhibitory sigmoid E_{max} effect model using WinNonlin 3.0 (Pharsight Corp., Mountain View, CA). BIS *versus* venous plasma propofol data were fit to the following equation: $E = E_{max} - (E_{max} - E_0) \cdot C^\gamma / (C^\gamma + EC_{50}^\gamma)$. Because BIS results represent signals averaged over a 30-s epoch, with a lag time for calculation, and were provided more frequently than blood was sampled, and because blood sampling also occurs over several seconds, we used the BIS value printed at the midpoint between the shortest blood sampling interval (*i.e.*, 30 s after the time the blood sample was initiated). Results are reported as EC₅₀ ± standard error of the estimate.

Wilcoxon signed-rank tests were performed for clinical end-points (times to: loss of response to voice command, loss of eyelash reflex, apnea, return of spontaneous ventilation, eye opening, and return of response to voice command). ANOVA was performed on BIS area under the percent decrement-*versus*-time curves (AUEC), maximum observed percent decrement (E_{max}), time to E_{max}, and time to return to baseline. Percent decrement at time *t* is defined as 100 × (baseline score - score at time *t*)/baseline score. Two-way repeated-measures

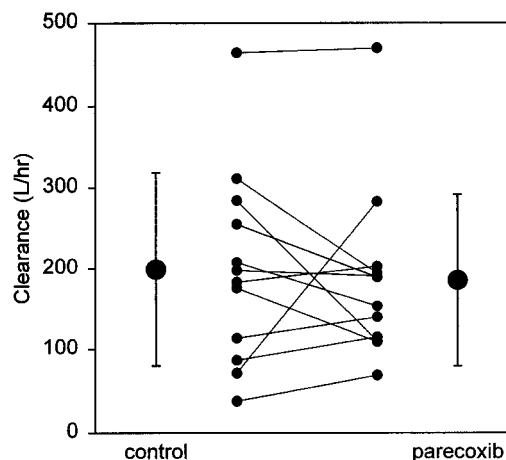


Fig. 4. Individual and mean (± SD) propofol clearance values (control *vs.* parecoxib).

Table 2. Propofol Clinical Effects

Time to Clinical Effect	Parecoxib + Propofol		Placebo + Propofol		P Value
	N	Mean ± SD	N	Mean ± SD	
Syringe drop (s)	12	37 ± 6	12	40 ± 9	0.634
Loss of response to command (s)	12	41 ± 5	12	41 ± 10	0.609
Apnea (s)	11*	54 ± 9	10*	54 ± 13	0.516
Return of spontaneous ventilation (s)	11*	208 ± 58	10*	217 ± 57	0.301
Eye opening (s)	12	380 ± 94	12	388 ± 82	0.569
Return of response to command (s)	12	398 ± 103	12	386 ± 75	0.556

* Some patients did not experience apnea after propofol administration.

ANOVA was performed on VAS, DSST, memory test using treatment and measurement times as factors, and their interactions. The Student-Newman-Keuls method for multiple comparison was used. Results are reported as mean ± SD. All statistical tests were performed at $\alpha = 0.05$ level.

Results

Mean and individual propofol plasma concentrations are presented in figures 2 and 3, respectively. Propofol pharmacokinetic parameters are listed in table 1. The ratios of the propofol geometric least squares means for plasma AUC, C_{max}, and CL values ranged from 0.900 to 1.005. No significant differences between parecoxib and control for propofol clearance (fig. 4) or any other propofol pharmacokinetic parameters were found. Pre-treatment with 40 mg intravenous parecoxib before propofol did not alter the anesthetic clinical end points (syringe drop, loss of response to voice command, loss of eyelash reflex, apnea) compared with placebo (table 2). Plasma concentrations of parecoxib and metabolites are presented in figure 5.

Bispectral Index scores after administration of parecoxib plus propofol were similar to those after administration of placebo plus parecoxib (fig. 6). The percent

decrement in BIS score at each time point was determined for each subject, and mean effect parameters were calculated (table 3). The mean area under the percent decrement-*versus*-time curves (AUEC) were similar for both treatments (8.6 vs. 7.6% decrement × h, $P = 0.644$). No significant differences were noted between treatments for any of the BIS parameters. The time to return to baseline was similar for both treatments (0.40 vs. 0.41 h, $P = 0.755$).

Digit-Symbol Substitution Test scores following administration of propofol after placebo and parecoxib are shown in figure 7. Mean DSST scores decreased to 54 and 60 in the parecoxib and placebo groups, respectively, at 15 min after propofol. After both treatments, mean DSST scores returned to baseline by 60 min after propofol administration. No significant difference between groups was seen between DSST scores at any time point. Memory scores are shown in figure 8. Fifteen minutes after propofol administration, mean scores decreased to 6 in both groups. No significant difference between groups was seen at any time point. VAS pharmacodynamic parameters are presented in figure 9. No significant difference in VAS scores between groups was seen at any time point.

The influence of parecoxib on propofol pharmacodynamics was determined by comparing BIS-propofol con-

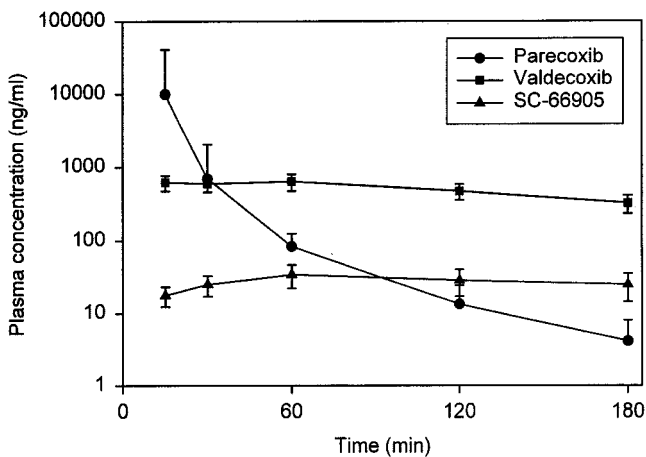


Fig. 5. Plasma concentrations of parecoxib and metabolites (mean ± SD, n = 12).

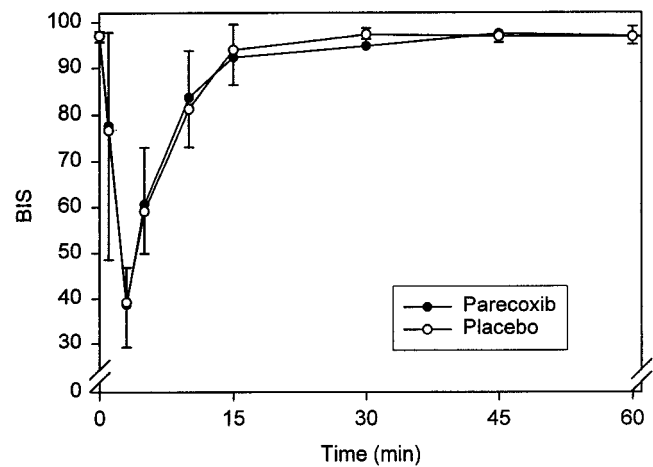


Fig. 6. Bispectral Index (BIS) scores after bolus propofol (parecoxib n = 11, placebo n = 12, mean ± SD).

Table 3. Bispectral Index Scores

Pharmacodynamic Parameter	Parecoxib + Propofol	Placebo + Propofol
AUEC (%decrement × h)	8.6 ± 4.6	7.6 ± 2.5
Emax (%decrement)	60.3 ± 8.4	63.5 ± 8.9
Time to Emax (h)	0.05 ± 0.005	0.04 ± 0.015
Time to return to baseline (h)	0.40 ± 0.30	0.41 ± 0.169

Percent decrement at time t is defined as 100 × (baseline score – score at time t)/baseline score.

AUEC = area under the percent decrement-versus-time curve; Emax = maximum observed percent decrement.

centration relations after parecoxib *versus* placebo (fig. 10). Data were fit to an inhibitory sigmoid Emax model. The propofol EC₅₀s for BIS effects (± standard error of the estimate) were 1.4 ± 0.3 and 1.2 ± 0.1 µg/ml, respectively, for parecoxib and placebo (*P* = not significant).

Discussion

Nonsteroidal antiinflammatory drugs inhibit prostaglandin synthesis and exert antiinflammatory and analgesic effects *via* inhibition of the enzyme cyclooxygenase.¹⁵ Cyclooxygenase exists as two isoenzymes: COX-1, the constitutive form, which is expressed in normal tissues and regulates the production of prostaglandins for homeostatic cell function; and COX-2, the inducible form, which is expressed in association with inflammation and pain. All currently available parenteral NSAIDs and conventional oral NSAIDs are nonspecific inhibitors of both COX-1 and COX-2. Currently, ketorolac tromethamine is the only parenteral NSAID available in the United States. Ketorolac is an effective analgesic but is associated with a significant incidence of untoward side effects, including upper gastrointestinal ulceration and bleeding, decrease in renal function, and platelet inhibition.¹⁶⁻¹⁸ Currently, available COX-2 selective in-

hibitors include celecoxib and rofecoxib, both administered orally. No parenteral COX-2 inhibitor is available.

Parecoxib is under development as a parenteral analgesic and antiinflammatory agent. Parecoxib has been found to have analgesic properties similar to those of ketorolac after oral surgery, hysterectomy, and orthopedic surgery³⁻⁵; however, it has a significantly lower incidence of untoward side effects. For example, the incidence of gastroduodenal ulcers with parecoxib was significantly lower than with ketorolac and no different than with placebo.¹⁹ Furthermore, parecoxib has not been found to inhibit platelet aggregation in response to arachidonate, in contrast to ketorolac.²⁰ Although fractional sodium excretion was decreased in subjects receiving parecoxib, the decrease was not as great as that observed in subjects receiving ketorolac.

Parecoxib is rapidly bioactivated to valdecoxib by amide hydrolysis of the sulfonamide propionate substituent.² Peak valdecoxib concentrations occur approximately 20 min after parecoxib injection. Valdecoxib can also be administered orally.²¹ Parecoxib hydrolysis in humans is mainly mediated by hepatic microsomal carboxylesterases, but parecoxib is stable in human plasma, suggesting that nonenzymatic hydrolysis and plasma esterases or amidases are not involved in amide hydrolysis to valdecoxib.² Valdecoxib is extensively metabolized in humans, with only 2% excreted unchanged in urine.⁶

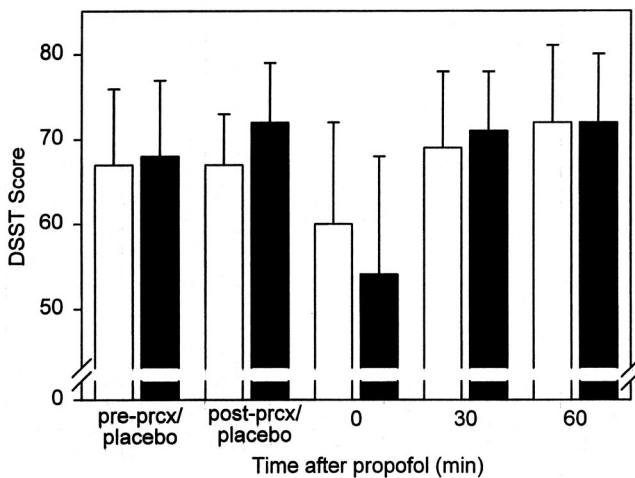


Fig. 7. Digit Symbol Substitution Test (DSST) scores after bolus propofol (mean ± SD, n = 12) following placebo (open bars) or parecoxib (prcx, solid bars) pretreatment.

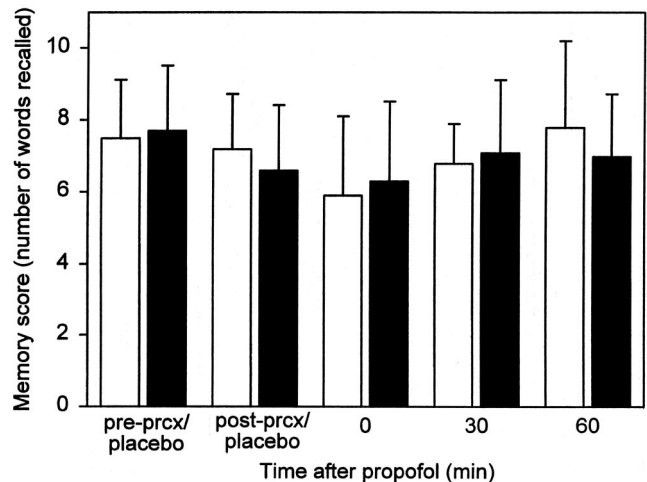


Fig. 8. Memory scores after bolus propofol (mean ± SD, n = 12) following placebo (open bars) or parecoxib (prcx, solid bars) pretreatment.

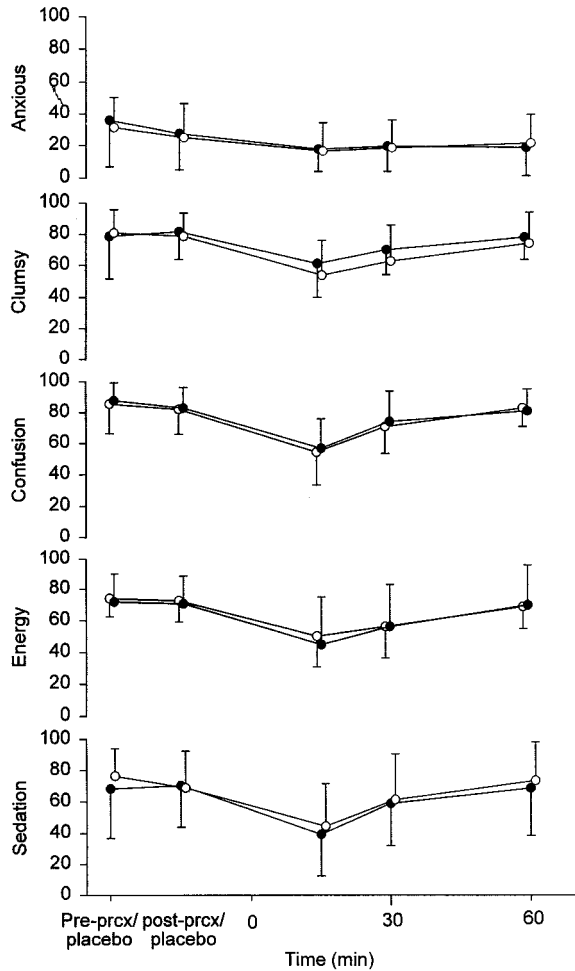


Fig. 9. Visual Analog Scale scores after bolus propofol (mean \pm SD, $n = 12$) following placebo (open circles) or parecoxib (prcx, solid circles) pretreatment.

The main route of valdecoxib phase I metabolism is hydroxylation of the methyl group on the isoxazole ring to form 1-hydroxyvaldecoxib (SC-66905), which is pharmacologically active. Plasma 1-hydroxyvaldecoxib concentrations are approximately one-tenth those of valdecoxib.⁶ Glucuronidation of 1-hydroxyvaldecoxib occurs at the alcohol (major) and sulfonamide (minor). Further oxidation of 1-hydroxyvaldecoxib yields an aryl hydroxide and its alcohol glucuronide. Valdecoxib also undergoes N-glucuronidation at the amino function of the sulfonamide group, which accounts for about 24% of overall valdecoxib metabolism.

Human liver valdecoxib hydroxylation is catalyzed primarily by CYP3A4, with a lesser contribution from CYP2C9, based on correlations with microsomal CYP3A4 activities, effects of isoform-selective inhibitors on microsomal valdecoxib metabolism, and metabolism by expressed CYPs.^{#6} Both parecoxib and valdecoxib

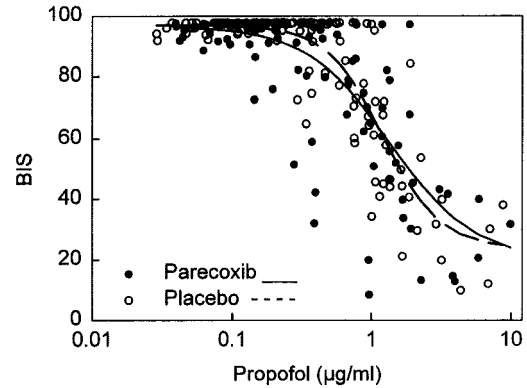


Fig. 10. Bispectral Index (BIS)–propofol concentration relations after parecoxib or placebo. Data points represent measured results. Lines show values predicted using parameters obtained using an inhibitory sigmoid Emax model.

have inhibitory effects toward CYP2C9. Apparent K_i values for parecoxib and valdecoxib, determined using various CYP2C9 substrates, were 2–13 μM (0.8–5 $\mu\text{g}/\text{ml}$) and 15–28 μM (5–9 $\mu\text{g}/\text{ml}$), respectively.[#] Maximal plasma concentrations of parecoxib and valdecoxib at relevant therapeutic doses are approximately 6.6 and 1.3 $\mu\text{g}/\text{ml}$, respectively; hence, it was prudent to assess the potential for an *in vivo* CYP2C9 drug interaction.

Propofol undergoes significant metabolism by CYP2C9 *in vitro*, and propofol hydroxylation is diminished by CYP2C9 inhibitors⁷ (although subsequent to the design and conduct of this investigation, CYP2B6 was also found to contribute to propofol metabolism^{22,23}). Therefore, we determined the effect of parecoxib on propofol disposition *in vivo*. The results showed that there was no clinically significant pharmacokinetic drug interaction between parecoxib and propofol. Plasma propofol disposition was similar between placebo and parecoxib-treated subjects, with no significant differences seen in C_{max} , clearance, elimination half-life, or volume of distribution. There was pharmacodynamic interaction between parecoxib and propofol, based on the absence of a difference between groups in clinical endpoints, BIS scores, DSST, memory, or VAS scores. Furthermore, parecoxib had no influence on propofol pharmacodynamics as determined by BIS–propofol concentration relations after parecoxib *versus* placebo. The current results are consistent with other concurrently determined findings that parecoxib did not affect the disposition of other CYP2C9 substrates. For example, coadministration of parecoxib with warfarin had no significant effect on prothrombin times compared with placebo, and parecoxib did not affect either R- or S-warfarin plasma disposition.[#]

There are limitations to this investigation. Plasma propofol concentrations change rapidly after a bolus dose; thus, effect site (brain) concentrations are better reflected by arterial than by venous concentrations. Nevertheless, venous propofol concentrations were nearly

[#] Pharmacia, Inc., unpublished data, June 2000; summary of the nonclinical pharmacokinetics and metabolism of parecoxib sodium.

identical in both groups; it is unlikely that arterial measurements would have shown a different result. Measuring depth of sedation with BIS during induction of anesthesia and rapidly changing propofol concentrations has not been validated. The BIS records data every 5 s but smoothes data over 30 s; thus, it is not capable of measuring the second-to-second changes that occur during induction of anesthesia. Furthermore, electroencephalographic effects lag behind arterial propofol concentrations (propofol $t_{1/2k_{eo}}$ of BIS was 2.3 min^{24}). However, because recovery from bolus propofol takes minutes rather than seconds, our investigation was able to use BIS to gauge rate of recovery. Finally, the effect of parecoxib on propofol pharmacokinetics during longer-term propofol administration was not evaluated and remains unknown.

Because parecoxib may be used preoperatively, before anesthetic induction and surgery, the possibility of drug-drug interactions with other anesthetics must be evaluated. Our investigation protocol was designed to comply with Food and Drug Administration guidelines.** The Food and Drug Administration recommends that metabolism of an investigational drug be defined during drug development and the possibility of drug interactions be investigated to assess adequate safety and effectiveness. Specifically, metabolic drug-drug interaction studies should explore whether an investigational agent may affect the metabolic elimination of marketed drugs and whether the interaction is sufficiently large to necessitate a dosage adjustment. When positive findings arise from *in vitro* studies, clinical studies are recommended because *in vitro* findings have limited ability to give a reliable quantitative estimate of the importance of a metabolic interaction. Hence, the propofol-parecoxib interaction was studied for two reasons. First, propofol is the only CYP2C9 substrate routinely used in anesthesia. Second, as the most commonly used intravenous induction agent, prudence and safety considerations warrant evaluation of a potential interaction with propofol.

In summary, these results show that single-bolus parecoxib, in doses expected to be used perioperatively, does not alter the disposition of bolus propofol. Single-bolus parecoxib does not alter the magnitude or the time course of bolus propofol clinical effects.

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** Guidance for Industry: In vivo drug metabolism/drug interaction studies: Study design, data analysis, and recommendations for dosing and labeling. Food and Drug Administration, November 1999. Available at: www.fda.gov/cder/guidance/2635fnl.pdf. Accessed July 2001.

References

- Jain KK: Evaluation of intravenous parecoxib for the relief of acute post-surgical pain. *Expert Opin Investig Drugs* 2000; 9:217-23
- Talley JJ, Bertenshaw SR, Brown DL, Carter JS, Graneto MJ, Kellogg MS, Koboldt CM, Yuan J, Zhang YY, Seibert K: N-[(5-methyl-3-phenylisoxazol-4-yl)-phenyl]sulfonamide, sodium salt, parecoxib sodium: A potent and selective inhibitor of COX-2 for parenteral administration. *J Med Chem* 2000; 43:1661-3
- Daniels SE, Kuss M, Mehlisch DR, Bauman A, Baum D, Karim A, Hubbard R: Pharmacokinetic and efficacy evaluation of intravenous parecoxib in a postsurgical dental pain model. *Clin Pharmacol Ther* 2000; 67:PI-8 (Abstract)
- Rasmussen GL, Steckner K, Hogue CW, Torri S, Kuss ME, Talwalker S, Hubbard RC: A comparative analgesic efficacy study of parecoxib sodium, a new injectable COX-2 specific inhibitor, in post-orthopedic surgery patients. *Proc Am Pain Soc* 2001; A776
- Kanaan CA, Bikhazi GB, Deepika K, Calfa CI, Ortiz K: Analgesic activity and safety of parecoxib in post-surgical patients: An interim report. *Anesth Analg* 2001; 92:S257
- Karim A, Laurent A, Slater ME, Kuss ME, Qian J, Crosby-Sessoms S, Hubbard RC: A pharmacokinetic study of intramuscular (IM) parecoxib sodium in normal subjects. *J Clin Pharmacol* 2001; 41:1-9
- Guitton J, Buronfosse T, Desage M, Flinois JP, Perdrix JP, Brazier JL, Beaune P: Possible involvement of multiple human cytochrome P450 isoforms in the liver metabolism of propofol. *Br J Anaesth* 1998; 80:788-95
- Crankshaw DP, Allt-Graham J: ED50 values for thiopentone, methohexital propomid, and Alfathesin: A clinical experiment. *Anaesth Intensive Care* 1978; 6:36-43
- Avram MJ, Sanghvi R, Henthorn TK, Krejcie TC, Shanks CA, Fragen RJ, Howard KA, Kaczynski DA: Determinants of thiopental induction dose requirements. *Anesth Analg* 1993; 76:10-7
- Smith RB, Kroboth PD, Vanderlugt JT, Phillips JP, Juhl RP: Pharmacokinetics and pharmacodynamics of alprazolam after oral and IV administration. *Psychopharmacology* 1984; 84:452-6
- Salthouse TA: What do adult age differences in the digit symbol substitution test reflect? *J Gerontol* 1992; 47:121-8
- Thorndike EL, Lorge I: *The Teacher's Word Book of 30,000 Words*. New York, Teacher's College Bureau of Publications, Columbia University, 1944
- Paivio A, Yuille JC, Madigan SA: Concreteness, imagery, and meaningfulness values for 925 nouns. *J Exp Psychol* 1968; 76:1-25
- Christian J, Bickley W, Tarka M, Clayton K: Measures of free recall of 900 English nouns: Correlation with imagery concreteness, meaningfulness, and frequency. *Mem Cogn* 1978; 6:379-90
- Kuehl FA, Egan RW: Prostaglandins, arachidonic acid, and inflammation. *Science* 1980; 210:978-84
- Feldman HI, Kinman JL, Berlin JA, Hennessy S, Kimmel SE, Farrar J, Carson JL, Strom BL: Parenteral ketorolac: The risk for acute renal failure. *Ann Intern Med* 1997; 126:193-9
- Gillis JC, Brogden RN: A reappraisal of its pharmacodynamic and pharmacokinetic properties and therapeutic use in pain management. *Drugs* 1997; 53:139-88
- Strom BL, Berlin JA, Kinman JL, Spitz PW, Hennessy S, Feldman H, Kimmel S, Carson JL: Parenteral ketorolac and risk of gastrointestinal and operative site bleeding. *JAMA* 1996; 275:376-82
- Jain KK: Evaluation of intravenous parecoxib for the relief of acute post-surgical pain. *Expert Opin Investig Drugs* 2000; 9:217-23
- Noveck RJ, Kuss ME, Qian J, North J, Hubbard RC: Parecoxib sodium, an injectable COX-2 specific inhibitor, does not affect aspirin-mediated platelet function [abstract]. *Reg Anesth Pain Med* 2001; 26(suppl 1):19
- Talley JJ, Brown DL, Carter JS, Graneto MJ, Koboldt CM, Masferrer JL, Perkins WE, Rogers RS, Shaffer AF, Zhang YY, Zweifel BS, Seibert K: 4-[5-Methyl-3-phenylisoxazol-4-yl]-benzenesulfonamide, valdecoxib: A potent and selective inhibitor of COX-2. *J Med Chem* 2000; 43:775-7
- Court MH, Duan SX, Hesse LM, Venkatakrisnan K, Greenblatt DJ: Cytochrome P-450 2B6 is responsible for interindividual variability of propofol hydroxylation by human liver microsomes. *ANESTHESIOLOGY* 2001; 94:110-9
- Oda Y, Hamaoka N, Hase I, Nakamot T, Asada A: Cytochrome P4502B6 is the principal isoform involved in the metabolism of propofol in vitro (abstract). *ANESTHESIOLOGY* 2000; 93:A537
- Kazama T, Ikeda K, Morita K, Kikura M, Doi M, Ikeda T, Kurita T, Nakajima Y: Comparison of the effect-site ke_0s of propofol for blood pressure and EEG bispectral index in elderly and younger patients. *ANESTHESIOLOGY* 1999; 90:1517-27
- Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P: Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *ANESTHESIOLOGY* 1997; 86:836-47
- Iselin-Chaves IA, Flaishon R, Sebel PS, Howell S, Gan TJ, Sigl J, Ginsberg B, Glass PA: The effect of the interaction of propofol and alfentanil on recall, loss of consciousness, and the bispectral index. *Anesth Analg* 1998; 87:949-55
- Chortkoff BS, Eger EI, Crankshaw DP, Gonsowski CT, Dutton RC, Ionescu P: Concentrations of desflurane and propofol that suppress response to command in humans. *Anesth Analg* 1995; 81:737-43