Communications to the Editor

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

John J. Talley,* Stephen R. Bertenshaw, David L. Brown, Jeffery S. Carter, Matthew J. Graneto, Michael S. Kellogg, Carol M. Koboldt, Jinhua Yuan,† Yan Y. Zhang, and Karen Seibert

Searle Research and Development, 700 Chesterfield Parkway, St. Louis, Missouri 63198, and 4901 Searle Parkway, Skokie, Illinois 60077

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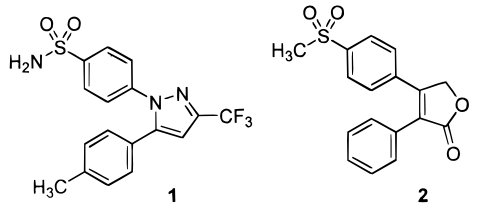
Introduction. Increased risk for gastrointestinal ulceration is associated with blockade of cyclooxygenase-1 (COX-1) derived prostaglandins.[1] Until very recently, all commercially available nonsteroidal antiinflammatory drugs (NSAIDs) were inhibitors of both COX-1 and COX-2. Selective inhibitors of COX-2 are now widely recognized as offering the promise of treatment of inflammatory conditions without the side effects associated with consumption of nonselective inhibitors.[2,3] Celecoxib (**1**)[4] and rofecoxib (**2**)[5] recently were the first two highly selective COX-2 inhibitors to be approved in selected markets for the treatment of certain inflammatory conditions.



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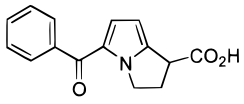

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To date, relatively few NSAIDs may be administered parenterally for the treatment of pain and inflammation. One of the most effective nonnarcotic analgesics for the treatment of moderate to severe acute pain, particularly postsurgical pain, is ketorolac (**3**).[6−8] Although very effective as an analgesic, ketorolac use is associated with a significant incidence of untoward side effects. The most common side effects associated with ketorolac consumption are increased risk for upper gastrointestinal ulceration and bleeding, particularly in the elderly; reduction of renal function, potentially leading to fluid retention and exacerbation of hypertension; and inhibition of platelet function, potentially predisposing to increased operative bleeding.[9−11] Ketorolac is a potent inhibitor of both COX-1 and COX-2.[12]

In general, COX-2 inhibitors of the diarylheterocycle class such as **1** and **2** possess modest aqueous solubility. This physicochemical characteristic restricts the dosing options available for this class of drug. In considering the development of a COX-2 inhibitor for parenteral administration, we wondered if a prodrug of a sulfonamide-based inhibitor could be designed which would possess the appropriate combination of aqueous solubility and in vivo antiinflammatory activity. Herein we describe our efforts that culminated in the identification of the injectable COX-2 inhibitor parecoxib sodium (**5b**).

Chemistry. Acylation of isoxazole sulfonamide **4** with an anhydride in the presence of triethylamine afforded the corresponding acylated sulfonamide. The sodium salt was then prepared by titration of the acylated sulfonamide with aqueous sodium hydroxide to afford the requisite sodium salts **5**, Scheme 1.

Results and Discussion. An important criterion that we established for a parenteral COX-2 inhibitor was for it to possess sufficient analgesic potency such that patients could be dosed with a minimal injection volume. Large injection volumes can be time consuming and may contribute to discomfort for patients. Meeting the criterion of a small injection volume dictated that only very potent compounds would be ideal for this application. Among the most potent and selective COX-2 inhibitors that have been identified is the isoxazole sulfonamide valdecoxib (**4**). Against recombinant human cyclooxygenase isoforms, **4** showed the following activity: hCOX-1 $IC_{50} = 140\ \mu M$ and hCOX-2 $IC_{50} = 0.005\ \mu M$. In addition, **4** possesses exceptional antiinflammatory activity in vivo.[13] Our strategy to develop an injectable COX-2 inhibitor commenced with the idea of identifying a water-soluble prodrug of **4** that would undergo biotransformation in vivo. To test whether an acylated sulfonamide[14,15] would serve as a prodrug for **4**, **5a** was prepared as described above and evaluated in vitro and in vivo. To our considerable satisfaction, the solubility of **5a** in phosphate-buffered saline at 25 °C was found to be quite substantial, 44 mg/mL. Against the recombinant isoforms of human cyclooxygenases, **5a** was found to show very weak inhibitory activity, hCOX-1 $IC_{50} \rightarrow 100\ \mu M$ and hCOX-2 $IC_{50} \rightarrow 20\ \mu M$. However, in the carrageenan air pouch model of inflammation,[16] **5a** showed potent antiinflammatory activity after intravenous, intramuscular, or oral administration, $ED_{50} = 0.5$ mg/kg.

The ample antiinflammatory activity of **5a** suggested that the acyl moiety was cleaved in vivo. To confirm this hypothesis, the pharmacokinetics and metabolic profile of **5a** were examined. It was found that the half-life for

* To whom correspondence should be addressed. Tel: 636-737-7373. Fax: 636-737-7425. E-mail: john.j.talley@monsanto.com.
† Searle Research and Development, Illinois.

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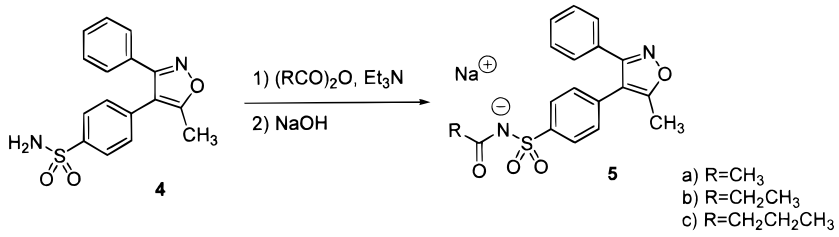
Scheme 1



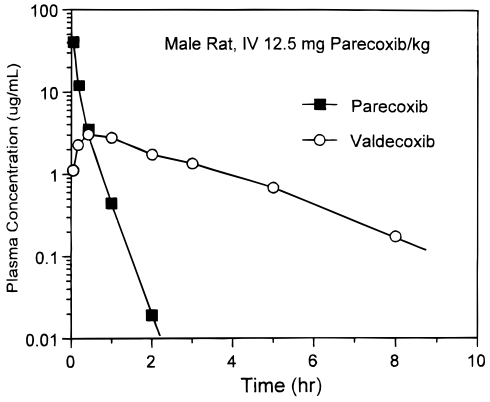


Figure 1. Pharmacokinetic profile of the conversion of parecoxib sodium (**5b**) (■) to valdecoxib (**4**) (○) in male rats.

the conversion of **5a** to **4** was about 15 min in rats. However, when **5a** was administered either intravenously or orally to canines or cynomolgus monkeys, it was found that **5a** was not completely converted to **4** and a significant amount of compound was eliminated in the urine unchanged. The attractive antiinflammatory activity of **5a** in rodents warranted evaluation of the congeners **5b** and **5c** in the rodent, dog, and monkey. Fortunately, in these three species both **5b** and **5c** were rapidly and completely converted to **4**. In addition, in vitro metabolic studies with human liver microsomes showed that both **5b** and **5c** were completely converted to **4**. Owing to the more favorable solubility of **5b** (22 mg/mL at 25 °C) versus **5c** (10 mg/mL at 25 °C) in phosphate-buffered saline, a more through assessment of the biological activity **5b** was conducted.

Pharmacokinetic studies of **5b** were conducted in vivo in the rat, dog, and cynomolgus monkey to determine the rate and extent of its conversion to **4**. The in vivo conversion of **5b** was complete and rapid after intravenous administration to male rats (mean elimination half-life = 0.135 ± 0.003 h), female dogs (0.553 ± 0.009 h), and female cynomolgus monkeys (1.21 ± 0.004 h). Shown in Figure 1 is the pharmacokinetic profile of **5b** in rodents. In vivo administration of **5b** demonstrated its bioequivalence to orally administered **4**. Chronic antiinflammatory activity was achieved in the rat adjuvant arthritis model, ED_{50} = 0.08 mg/kg.[17] Acute antiinflammatory activity of **5b** was demonstrated in the carrageenan air pouch assay, 98% inhibition at 0.3 mg/kg.

Intravenous administration of **5b** showed considerable activity in an acute analgesic assay (carrageenan foot pad edema).[18,19] The analgesic efficacy as well as the onset of action of **5b** was assessed in a therapeutic paradigm.[8] Three hours after administration of carrageenan to the hind foot pad of rats results in maximal edema and pain response. When edema and pain

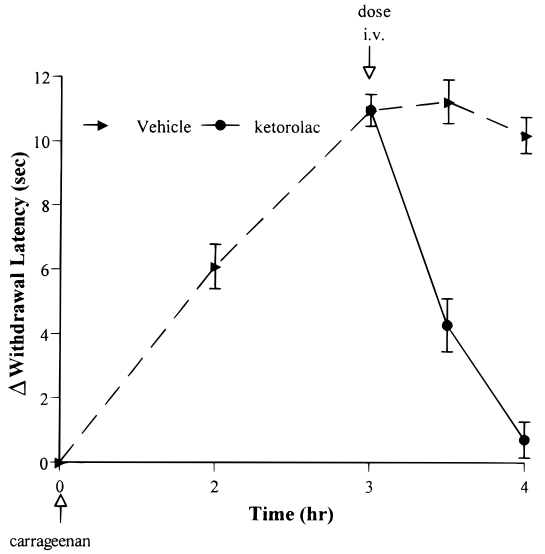


Figure 2. Time course for the reversal of hyperalgesia and prostaglandin production after intravenous administration of ketorolac (**3**).

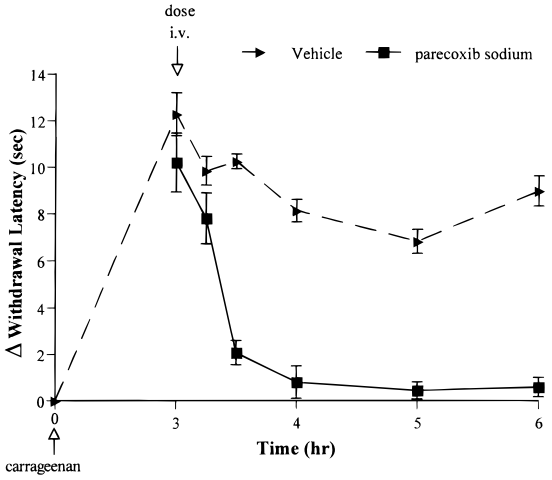


Figure 3. Time course for the reversal of hyperalgesia and prostaglandin production after intravenous administration of parecoxib sodium (**5b**).

reached a maximal response, **5b** was administered intravenously and the reversal of hyperalgesia measured. Shown in Figures 2 and 3 are the results of administration of 30 mg/kg ketorolac compared with the same dose of **5b**. When dosed therapeutically, ketorolac (30 mg/kg) rapidly and completely inhibited the pain response. The activity of **5b** at 30 mg/kg in this model compared favorably with the activity of ketorolac, producing a complete blockade of the carrageenan-induced hyperalgesia within 1 h after intravenous administration (Figure 3). The ED_{50} for **5b** in this model was 5 mg/kg, with a maximal analgesic response

achieved within 1 h of administration, indicating that it possesses a potent and fast-acting analgesic pharmacological profile.

Conclusions. The availability of a safe and efficacious injectable COX-2 inhibitor for acute pain management, particularly postsurgical pain, constitutes an important unmet medical need. Parecoxib sodium, **5b**, a water-soluble prodrug of valdecoxib, **4**, was identified as a highly potent and selective inhibitor of PGs from COX-2. In a therapeutic model of acute pain, parecoxib sodium showed excellent efficacy and a rapid onset of action comparable with the most potent analgesic NSAID ketorolac. Parecoxib sodium is currently in clinical evaluation for the management of acute pain.

Supporting Information Available: Biological procedures, synthetic procedures, and spectral data for compounds **5a**−**5c** are available free of charge via the Internet at http://pubs.acs.org.

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