Central Nervous System Concentrations of Cyclooxygenase-2 Inhibitors in Humans

Gregory Dembo, M.D.,* Sang B. Park, Ph.D.,† Evan D. Kharasch, M.D., Ph.D.‡

**Background:** Cyclooxygenase-2 (COX-2)-selective inhibitors (coxibs) are under investigation for the potential therapy, attenuation, or prevention of neuroinflammatory and neurodegenerative disorders. Coxibs are also a significant advance in pain therapy and are traditionally considered to achieve analgesia via peripheral effects. However, in animals, central nervous system (CNS) COX-2 activity and prostanoid concentrations are increased by peripheral inflammation, central sensitization has been proposed to account for long-term pain-related phenomena, and coxibs achieve significant cerebrospinal fluid (CSF) concentrations and may cause analgesia via CNS action. Nevertheless, it remains unknown whether or which coxibs reach the CNS in humans. This investigation determined whether coxibs can reach the CNS in humans, based on CSF concentrations.

**Methods:** Ten healthy human volunteers simultaneously received a single oral dose of celecoxib (200 mg), rofecoxib (50 mg), and valdecoxib (40 mg). Blood and CSF were serially sampled for 10 h, and plasma total and unbound and CSF coxib concentrations were quantified by mass spectrometry.

**Results:** Total plasma concentrations and time to maximum plasma concentration were similar among the three coxibs. In contrast, unbound (free) plasma concentrations differed significantly. Maximum unbound plasma concentrations were 1.4 ± 0.5, 42 ± 17, and 6.0 ± 2.9 ng/ml, respectively, for celecoxib, rofecoxib, and valdecoxib. COX-2 inhibitors rapidly penetrated the CNS. Maximum CSF concentrations were 2 ± 2, 557 ± 25, and 10 ± 4 ng/ml, respectively, for celecoxib, rofecoxib, and valdecoxib. CSF concentrations exceeding the median inhibitory concentration for COX-2 were achieved by rofecoxib and valdecoxib but not celecoxib.

**Conclusions:** These results show that coxibs do reach the CNS in humans, with rapid penetration, and in concentrations apparently sufficient to inhibit COX-2 activity. There were significant differences among coxibs in CSF penetration. Unbound (free) plasma coxib concentration was the major determinant of CSF concentration. This supports the hypothesis that coxibs may act, in part, in the human CNS, provide important new information on the mechanism and treatment of pain and may guide coxib selection for therapeutic trials when CNS penetration is desirable.

Cyclooxygenase-2 (COX-2) inhibitors are a recent significant advance in the treatment of pain, including acute perioperative pain, which is notoriously undertreated. COX-2 inhibitors (coxibs) can alone relieve mild postoperative pain, decrease by 20-50% the dose of opioids required to treat moderate to severe pain, decrease pain even in patients who can self-administer opioids to maximum satisfaction, decrease opioid-related side effects, and provide greater patient satisfaction compared with placebo. The primary advantage of coxibs, compared with nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), is their lack of effect on platelet function and bleeding. This confers the opportunity for administration preoperatively, to prevent the release of inflammatory mediators that initiate the pain cascade, rather than postoperatively after the cascade is triggered. Nevertheless, the mechanism by which COX-2 inhibitors provide perioperative analgesia is unknown. A significant unresolved question regarding the mechanism of coxib analgesia is the relative contribution of action at peripheral versus central nervous system (CNS) targets.

Some information suggests a CNS role for coxibs in eliciting analgesia. Inflammatory pain is the response to surgical or other trauma. Peripheral and central sensitization, and CNS neuronal plasticity, are considered pivotal in the pathogenesis of postinjury pain, particularly in the transition from acute to chronic pain. In animals, CNS prostanooids are responsible for a substantial fraction of the hyperalgesia and allodynia that characterize postinjury hypersensitivity, the role of CNS COX-2 in mediating such pain has recently been identified, and inhibition of CNS COX-2 nociceptive pathways may be a significant mechanism of analgesia. In rodents, COX-2 is up-regulated in the spinal cord and brain in response to nerve injury, leading to increased spinal cord prostaglandin (PG) E2 synthesis and CSF concentrations, and thence to central sensitization, allodynia, and hypersensitivity, whereas COX-2 inhibition prevented the increase in spinal cord PGE2 concentrations caused by painful paw inflammation and attenuated the pain response. Furthermore, PGE2 regulates long-term hippocampal signaling and plasticity in animals. An analogous role for PGE2 in humans might explain the development of acute or chronic pain. Interestingly, CSF concentrations of the principle metabolite of prostacyclin (6-keto-PGF1α) were increased after thoracotomy, and this increase was suppressed by the selective COX-2 inhibitor nimesulide, although PGE2 was not evaluated. Although it has traditionally been considered that up-regulation and expression of spinal cord COX-2 is required for NSAID and coxib analgesia, thereby constituting a “late” response.
new animal data show that constitutive spinal cord COX-2 expression seems greater than previously appreciated, and inhibition of constitutive COX-2 immediately after injury (before COX-2 up-regulation) decreased injury-related neuronal activation and hyperalgesia. Thus, coxibs can have immediate effects, suggesting that blockade of constitutive COX-2 before tissue injury might reduce both peripheral and central sensitization.

Although it is attractive to posit that NSAIDs and coxibs work analogously in the human CNS to inhibit COX-2 and produce analgesia, it is virtually unknown when or even whether they reach therapeutic concentrations in the human CNS. In rodents, systemic administration of celecoxib and rofecoxib produced spinal cord and CSF concentrations exceeding the median COX-2 inhibitory concentration (IC50). A single CSF sample did reveal the presence of rofecoxib in human CSF, although the time course of such penetration remains unknown, as does the comparative CNS penetration of the various coxibs. The veracity of the notion of central sensitization and its response to coxibs in humans depends on the demonstration that coxibs reach therapeutic concentrations in the human CNS. However, this remains unknown.

The therapeutic value of COX-2 inhibitors is not limited to arthritic inflammation, pain, and analgesia. There is accumulating and compelling evidence that COX-2 actively participates in the pathogenesis of ischemic brain injury and the development and progression of neurodegenerative diseases such as Alzheimer disease, Parkinson disease, and amyotrophic lateral sclerosis. Moreover, COX-2 inhibition holds promise in the potential attenuation, prevention, and therapy of these neuroinflammatory and neurodegenerative disorders, and numerous clinical trials involving coxibs are ongoing or planned. The two most common types of brain tumor (gliomas and meningiomas) overexpress cyclooxygenases, and COX-2 inhibitor efficacy against these malignant tumors is currently under clinical investigation. Nonetheless, there is currently no information, specifically on the CNS access of coxibs, to guide the rational selection of which of the many available COX-2 inhibitors to evaluate in these CNS disease trials. Moreover, the factors that determine coxib access to the human CNS remain unidentified.

The purpose of this clinical investigation was to test the hypothesis that COX-2 inhibitors (celecoxib, rofecoxib, and valdecoxib) penetrate the CNS in humans, as evidenced by measurable CSF concentrations. In addition, the relative CNS dispositions of these three coxibs were compared.

Materials and Methods

Protocol

This was a nonrandomized, single-session clinical study. Ten normal healthy volunteers (6 men and 4 women; age 25 ± 4 yr; weight, 73 ± 14 kg) were studied after providing written informed consent approved by the University of Washington Institutional Review Board (Seattle, Washington). Exclusion criteria included an allergy to any COX-2 inhibitor or aspirin, history of renal insufficiency or hepatic disease, pregnancy, and use of drugs, foods, or natural products known to affect cytochrome P-450s 2C or 3A. Subjects were instructed to consume no ethanol or caffeine-containing products for at least 24 h before the study and fasted for at least 8 h before the study. A peripheral intravenous catheter was placed for blood sampling. Subjects had a 24-gauge spinal microcatheter (SIMS Portex Inc., Keene, NH) placed in the lumbar CSF via a 19-gauge Special Sprotte needle (Pajunk GmbH, imported by PNA Medical Systems, Glens Falls, NY) inserted at the L2–L3 level during lidocaine local anesthesia using a standard sterile technique.

After obtaining baseline blood and CSF samples, subjects simultaneously received 200-mg celecoxib tablets, 50 mg rofecoxib elixir, and 40-mg valdecoxib tablets with sips of water. The rationale for administering all three coxibs together was that, using selective assay techniques, the CSF and plasma concentrations of all three drugs could be determined simultaneously, thereby decreasing the number of study sessions needed from three to one, and eliminating interday variability as a potential confounder. There was no additional risk to simultaneous coxib administration, because high-dose (i.e., 10-fold higher than the typical dose) coxib administration has been shown to be safe.

Venous blood and CSF samples were obtained before and 0.5, 1 1.5, 2, 3, 4, 5, 6, 7, 8, and 10 h after drug administration. Blood samples were centrifuged, and plasma was removed and, together with the CSF samples, stored at −20°C until analyzed. Subjects remained supine for the study. They received a standard meal 4 h after drug dosing and had regular meals and free access to food thereafter. The spinal catheter was removed, and subjects remained supine for another 4 h to decrease the potential incidence of postdural puncture headache. Because of catheter malfunction, CSF was not obtained from one subject.

Analytical Methods

Valdecoxib was a gift from Pfizer, Inc. (New York, NY), and rofecoxib and celecoxib were prepared from commercial tablets. The tablet was ground to fine powder, dissolved in 0.1M sodium acetate (pH 5.0), extracted with two volumes of ethyl acetate, dried over magnesium sulfate, and evaporated in vacuo to give a white powder. Purity and identity of the inhibitors was assessed by high-pressure liquid chromatography with ultraviolet detection, liquid chromatography–mass spectrometry (LC-MS), 1H nuclear magnetic resonance spectrometry, and elemental analysis.

Plasma and CSF coxib concentrations were quantified by liquid–liquid extraction and LC-MS. CSF (1 ml) or plasma (0.5 ml), internal standards stock (50 ng nimesu-
liday and 50 ng ketoprofen in methanol, 100 μl for CSF and 50 μl for plasma). 0.1 m sodium acetate (pH 5.0; 0.5 ml for plasma, 1 ml for CSF), and 1:1 dichloromethane/hexane (3 ml for plasma, 4 ml for CSF) were added to a glass tube, vortexed, and centrifuged, and the organic phase was removed and evaporated to dryness under a nitrogen stream. The residue was reconstituted in 60 μl acetonitrile:10 mM ammonium acetate (pH 5.0) (3:7) and analyzed by LC-MS, which was an Agilent Series 1100 with a Truesphere C18 HPLC column (2.1 × 150 mm, 3 μ; Poulter Sci. Inc., CA) and C18 guard column (2.0 × 4.0 mm, 5 μ; Phenomenex, CA). The mobile phase was acetonitrile:10 mM ammonium acetate (pH 5.0) at 0.25 ml/min. The gradient started at 30% acetonitrile, increased linearly to 90% over 14 min, and then returned to 30% acetonitrile to reequilibrate (total run time 22 min). The mass spectrometer was operated in negative electrospray ionization mode with selected ion monitoring. The retention times and ions monitored were ketoprofen (7.2 min, M-H m/z 253.1), rofecoxib (8.6 min, M-H m/z 313.1), valdecoxib (9.7 min, m/z M-H 307.1), and celecoxib (14.0 min, M-H m/z 380.1). The capillary voltage was 3.5 kV, with nitrogen drying gas at 6 l/min and 350°C, nebulizer pressure of 35 pounds per square inch gauge (psig), and fragmentor voltage of 70 V. All relevant instrument parameters were optimized for maximal sensitivity. Calibration curves were obtained by analyzing drug-free plasma and CSF to which were added the coxibs (1–100 ng/ml celecoxib, 10–1,000 ng/ml rofecoxib, and 2–1,000 ng/ml valdecoxib in plasma and 0.5–100 ng/ml celecoxib, 5–100 ng/ml rofecoxib, and 0.5–100 ng/ml valdecoxib in CSF). Quality control (QC) samples in plasma (10 and 100 ng/ml for each coxib) and CSF (5 and 50 ng/ml for each coxib) were prepared, aliquotted, and analyzed daily with the analytical samples. Standard curves (unweighted) were linear (r² > 0.98 for both plasma and CSF). Limits of quantification were 0.5, 5, and 0.5 ng/ml in CSF and 1, 10, and 2, ng/ml in plasma for celecoxib, rofecoxib, and valdecoxib, respectively. Interday coefficients of variation were lower than 15% for plasma and 14% for CSF.

Coxib protein binding was determined by ultrafiltration. To determine free plasma concentrations, plasma (0.5 ml) was centrifuged in an Amicon Centrifree YM-30 (Millipore, Bedford, MA). The filtrate (0.25 ml) was collected, and 25 μl internal standards stock, 0.25 ml sodium acetate (0.1 m, pH 5.0), and 1:1 dichloromethane/hexane (2 ml) were added. The sample was then processed as described above.

Statistical Analysis

Maximum concentrations and times to maximum concentration were determined visually. Differences between treatment groups were evaluated by repeated-measures analysis of variance (SigmaStat 3.01; SPSS, Chicago, IL).

Results

Cyclooxygenase-2 inhibitor disposition in plasma, as well as maximum concentrations and time to maximum concentrations, were comparable to previous reports (fig. 1).29–31 There were no significant differences among celecoxib, rofecoxib, and valdecoxib in their maximum plasma concentrations (548 ± 339, 494 ± 236, and 450 ± 208 ng/ml, respectively; fig. 1A) or time to maximum plasma concentration (2.7 ± 1.7, 2.9 ± 1.2, and 3.1 ± 1.9 h, respectively). Coxib elimination was not formally evaluated (i.e., sampling was not continued for at least 24 h) because this has been well described previously, and the focus of the current investigation was on uptake and CSF kinetics.

All three coxibs were found in CSF (fig. 2). The maximum CSF concentrations (2.4 ± 2.2, 56.6 ± 24.8, and 9.7 ± 4.4 ng/ml, respectively, for celecoxib, rofecoxib, and valdecoxib) differed markedly and significantly among the three drugs. In contrast, times to first quantifiable CSF concentrations (1.7 ± 0.8, 0.9 ± 0.3, and 1.3 ± 0.8 h, respectively) and times to maximum CSF concentration (4.3 ± 2.4, 4.4 ± 1.1, and 4.8 ± 1.6 h, respectively) for celecoxib, rofecoxib, and valdecoxib did not differ significantly.

Cerebrospinal fluid coxib concentrations can be compared with those required for COX-2 inhibition, to place
these findings in context. The IC$_{50}$ values for expressed COX-2 inhibition are 15, 6, and 1.6 ng/ml for celecoxib, rofecoxib, and valdecoxib, respectively. CSF rofecoxib and valdecoxib concentrations equal to or exceeding the IC$_{50}$ for COX-2 inhibition occurred throughout the entire measurement period, and concentrations exceeding the IC$_{50}$ were rapidly achieved (within 0.9 ± 0.3 and 1.8 ± 1.4 h, respectively, for rofecoxib and valdecoxib; P > 0.05). Peak CSF concentrations of these two drugs were 10 and 6 times their IC$_{50}$ for COX-2 inhibition (P < 0.05 vs. rofecoxib and valdecoxib). In contrast, CSF celecoxib concentrations remained less than 15% of the IC$_{50}$ for COX-2 inhibition.

Relative coxib penetration into the CNS is indicated by the CSF:plasma concentration ratio (fig. 3). It was serendipitous, rather than intended, that plasma concentrations of the three coxibs were similar (fig. 1A). Nonetheless, it does magnify differences (fig. 2) among the coxibs in their CNS penetration. Figure 3A shows clear differences among the three coxibs in the CSF penetration of total drug in plasma. There was also a time-dependent increase in the CSF:total plasma concentration ratio, which continued to increase even while plasma coxib concentrations were declining. Maximum CSF:total plasma concentration ratios were not achieved for approximately 6 h (0.008 ± 0.004, 0.20 ± 0.12, and 0.040 ± 0.032, for celecoxib, rofecoxib, and valdecoxib, respectively; P < 0.05).

Coxibs are highly bound to plasma proteins. Some consider that only unbound (non–protein-bound) drug in blood has access to the CNS. Hence, protein binding was determined in each subject. Protein binding averaged 99.7 ± 0.1, 90.7 ± 4.0, and 98.3 ± 0.6%, respectively, for celecoxib, rofecoxib, and valdecoxib, similar to that reported previously. Protein binding results were used to calculate free (unbound) coxib concentrations in each subject (fig. 1B) and thence the CSF:unbound plasma concentration ratio (fig. 3B). There were significant differences among the coxibs in their unbound plasma concentrations (fig. 1B). Maximum unbound plasma concentrations were 1.4 ± 0.5, 4.2 ± 17, and 6.0 ± 2.9 ng/ml, respectively, for celecoxib, rofecoxib, and valdecoxib. In contrast, there were no differences in the CSF penetration of unbound coxibs in plasma (fig. 3B). There was also a time-dependent increase in the CSF:unbound plasma ratio, similar to that for the CSF:total plasma ratio. For all coxibs, the average CSF:unbound plasma ratio over the measurement period was 1.5–1.7.

The total coxib dose administered in this investigation was greater (2.5-fold) than typical therapeutic doses. Nonetheless, as anticipated, there was no additional risk, because high-dose COX-2 inhibitor administration (i.e., up to 10-fold higher than typical clinical doses) has been shown to be safe. There were no coxib-related adverse events in the protocol. Two subjects, both female, experienced post–dural puncture headaches, which were treated with an epidural blood patch.

Discussion

The results of this investigation clearly demonstrate that clinically available COX-2 inhibitors do penetrate the CNS in humans, evidenced by their appearance in CSF, and in concentrations apparently sufficient to inhibit the activity of CNS COX-2 enzyme. Furthermore, these therapeutic CSF coxib concentrations were sustained. This is apparently the first report that valdecoxib and celecoxib are found in human CSF, which concurrently compares the systemic and CNS disposition of
multiple COX-2 inhibitors in the same subject and which shows the human CSF concentration time course of any COX-2 inhibitor.

The time courses of absorption and systemic disposition of the three coxibs were very similar. In contrast, there were unambiguous differences in the CNS penetration of the three coxibs, with rofecoxib and valdecoxib having significantly greater CNS penetrations (26- and 5-fold greater, respectively, based on the maximum CSF:total plasma concentration ratio) than celecoxib. Differences among coxibs in their CNS penetration were not related to differences in total plasma concentration. Rather, they were related to plasma free (unbound) concentration. Indeed, CSF concentrations, when normalized to unbound coxib concentrations, were identical for the three drugs. Thus, for celecoxib, rofecoxib, and valdecoxib, the major determinant of human CNS penetration is plasma protein binding, or free (unbound) concentration.

There was an approximately 2-h delay between peak plasma and CSF coxib concentrations. It is unlikely that this entirely represents the transit of coxib-containing CSF from the brain to the lumbar space (vide infra). Rather, this likely also reflects coxib transport from the blood to the CSF through the choroid plexus (vide infra). The mechanism of coxib transport into the CNS merits further investigation.

One study previously evaluated, at a single time point and for a single COX-2 inhibitor (rofecoxib), a coxib concentration in human CSF.21 Plasma and CSF rofecoxib concentrations approximately 1–2 h after dosing were 503 ± 198 and 33 ± 13 ng/ml, respectively, and the CSF:total plasma concentration ratio was 0.073 ± 0.03. These observations are consistent with the current results. In contrast, in rats, CSF rofecoxib concentrations were reported to be 35% of the plasma concentration, questioning the applicability of this model to human coxib disposition.

The role of plasma protein binding in coxib CNS penetration is interesting. It was formerly considered that only unbound drug had access to the CNS, that brain extracellular fluid concentrations approximated free (unbound) blood concentrations, and hence that one needed only to measure free drug concentration in blood to know brain concentrations.34 Nonetheless, it is now accepted that protein binding can be restrictive (limiting CNS drug access) or nonrestrictive (particularly if dissociation from plasma protein binding is significant relative to the rate for brain uptake). For the three coxibs studied, unbound plasma concentration was the major determinant of CNS penetration. This information may be useful in the development of new coxibs, particularly if high CNS concentrations are desired. It is interesting to note that the protein binding of sulfonamide COX-2 inhibitors such as celecoxib and valdecoxib (> 98%) is greater than that of methylsulfone COX-2 inhibitors such as rofecoxib and etoricoxib (approximately 90%).35 The physicochemical features that account for these differences and whether they bear on the CNS penetration of various COX-2 inhibitors remain to be determined, although valdecoxib and rofecoxib are less lipophilic than celecoxib.

Central sensitization, the involvement of COX-2 and PGE2, and the response to coxibs are well established in animals.8,12,13 The concept of central sensitization and the role of COX-2 and PGE2 and the response to coxibs in humans are less well established and depended in part on the demonstration that coxibs could reach therapeutic concentrations in the human CNS. Absent such concentrations, a role for CNS COX-2 inhibition in the mechanism of coxib analgesia would not be supported. The current results, showing that clinically available COX-2 inhibitors do penetrate the CNS in humans in concentrations apparently sufficient to inhibit the activity of CNS COX-2 enzyme, provides support for a role for CNS COX-2 inhibition in the mechanism of coxib analgesia.

If CNS COX-2 inhibition is mechanistically significant, the current results may guide the selection of which coxib to use clinically for the treatment of pain. In addition, numerous clinical trials evaluating the prophylactic or therapeutic efficacy of coxibs in ischemic brain injury; the development and progression of neurodegenerative diseases such as Alzheimer disease, Parkinson disease, and amyotrophic lateral sclerosis; and malignant brain tumors are ongoing or planned,22–26 albeit in the absence of knowing which coxibs achieve meaningful CNS concentrations in human. The current result may be applicable to coxib selection for such studies.

The blood–brain barrier (BBB) and the blood–cerebrospinal fluid barrier (BCSFB) are the two main interfaces between the systemic circulation and the CNS (fig. 4).36,37 Because the surface area of the BBB is 1,000- to 5,000-fold greater than that of the BCSFB, the BBB is considered the predominant route of drug access to the...
CNS. The BBB is defined by cerebral capillary endothelial cells, connected by tight junctions that limit paracellular permeability, which lie on a basement membrane. The BSCFB is located at the choroid plexus, which protrudes into the third and fourth ventricles and is defined by epithelial cells connected by tight junctions that limit paracellular permeability. Ependymal cells, connected by tight junctions, separate the brain from the CSF, and there is little net drug exchange via this pathway. The fundamental assumption in this investigation is that CSF COX-2 inhibitor concentration (essentially free drug concentration because there is minimal protein in CSF to bind drug) is a reliable surrogate for the concentration of unbound drug in the brain or spinal cord extracellular fluid, in turn approximating the actual parenchymal (active site) drug concentration—specifically, that drug transport across the BCSFB approximates drug transport across the BBB, and hence CSF sampling can inform brain concentrations. The similarities between the BBB and BCSFB support this approach. For example, there are tight junctions between the capillary endothelial cells of the BBB and the epithelial cells of the BCSFB. Lipophilic drugs, such as COX-2 inhibitors, penetrate both the BBB and the BCSFB mainly by transcellular diffusion (as compared with paracellular diffusion which predominates for hydrophilic drugs).

Cerebrospinal fluid sampling is a generally viable technique for assessing drug penetration into the CNS. Although direct comparisons of drug concentrations in the brain, CSF, and plasma are scarce, CSF for many drugs is considered to be pharmacokinetically indistinguishable from the site of action. Indeed, for barbiturates, theophylline, and 1,4-substituted benzodiazepines, CSF was in close equilibrium with the effect compartment, and CSF concentrations were predictive of pharmacologic activity.

However, potential limitations of assuming that lumbar CSF COX-2 inhibitors concentrations reflect brain concentrations are recognized. (1) There are differences between the BBB and the BCSFB, in that the capillaries of the former are restrictive whereas those of the latter are permeable (the barrier function is maintained by the epithelial cells). (2) Tight junctions of the BCSFB are slightly more permeable than those of the BBB. (3) There may be potential differences between the BBB and the BCSFB in the number and role of drug influx and efflux transporters. (4) Drug concentrations may not be homogeneous throughout the CSF and may be affected by CSF turnover. (5) There is a delay between drug entry into brain CSF and the appearance of that CSF for lumbar sampling (approximately 10–15 min, based on CSF transit of approximately 1 mm/s). Thus, potential limitations of lumbar CSF sampling are acknowledged. Nonetheless, absent any information other than plasma coxib concentrations, this potential limitation is relatively minor, and CSF coxib concentrations are clearly informative.

The current investigation assessed CNS and CSF disposition of a single dose of each coxib. Further investigation is required to determine CNS disposition and CSF concentrations of coxibs after chronic administration and steady state conditions.

In summary, this is the first investigation to show that clinically available COX-2 inhibitors do penetrate the CNS in humans in clinically meaningful and sustained concentrations; that the time course of absorption and systemic disposition of the three coxibs was similar; and that there were significant differences in coxib CNS penetrations, with rofecoxib and valdecoxib having significantly greater CNS penetration, and these differences are related to plasma protein binding. These results may be useful in the therapeutic use of these versatile drugs.


