Pharmacokinetics of Celecoxib after Oral Administration in Dogs and Humans: Effect of Food and Site of Absorption

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ABSTRACT

Celecoxib pharmacokinetics was evaluated after single and multiple oral dosing; after dosing in a solution and as a solid; with and without food; and after administration into different sites of the GI tract using dog. After oral dosing in a solution, celecoxib was rapidly absorbed and reached maximum concentrations by 1 h; absorption was delayed another 1 to 2 h when administered as a solid. The absolute bioavailability of celecoxib was higher when given as a solution (64–88%) compared with capsule (22–40%). The absorption of celecoxib given in a capsule was delayed by food, although systemic exposure increased by 3- to 5-fold. The systemic availability of celecoxib given intragastrically in solution was similar to that obtained following direct instillation into the duodenum, jejunum, or colon through a chronic intestinal access port. Collectively, these data suggest that celecoxib is a highly permeable drug that can be absorbed throughout the GI tract and that dissolution may be a rate-limiting factor for absorption from solid dosage forms. Unlike dogs, celecoxib given to humans with a high fat meal exhibits only a slight increase in AUC0–t (11%) that is not clinically significant with regard to safety or efficacy. In humans, a lower dose and a longer GI residence time may promote the opportunity for absorption of a poorly soluble drug such as celecoxib that can be absorbed throughout the GI tract. This would minimize the effect of food on absorption; as such, patients with arthritis can be given celecoxib with or without food.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to treat the signs and symptoms of inflammation associated with rheumatoid arthritis and osteoarthritis. However, side effects related to gastrointestinal, renal, and platelet function sometimes have important clinical limitations on NSAID use (Borda and Koff, 1992). Since the early 1970s, the mechanism of action of NSAIDs has been attributed to the blockade of the production of prostaglandins via inhibition of the enzyme cyclooxygenase (Smith and Willis, 1971; Vane, 1971). The existence of two cyclooxygenase(s), designated COX-1 and COX-2, has been reported (Masferrer et al., 1994; Needleman and Isakson, 1997). COX-1, the constitutive form, is expressed in most tissues, including the gastrointestinal tract and platelets and produces prostaglandins necessary for normal physiological function (Kujubu et al., 1991; Xie and Chipman, 1991). COX-2 is inducible and is predominantly expressed in association with inflammation (Raz et al., 1988; Masferrer et al., 1994). It has been demonstrated that COX-2-specific inhibitors will have anti-inflammatory activity without the associated GI side effects of traditional NSAIDs (Simon et al., 1999; Silverstein et al., 2000).

Celecoxib is a marketed COX-2-specific inhibitor that does not inhibit COX-1 at the clinical dose used to treat osteoarthritis and rheumatoid arthritis (Isakson et al., 1998).

Celecoxib (Fig. 1) is extensively metabolized in humans and is excreted primarily as metabolites (Paulson et al., 2000a). The methyl group of celecoxib is oxidized to the hydroxymethyl metabolite, followed by further oxidation of the hydroxyl metabolite to the carboxylic acid. Glucuronide conjugation of the carboxylic acid metabolite is a minor pathway of elimination in humans.

The metabolism of celecoxib across several species, including mouse, rat, rabbit, dog, and monkey, has been shown to be similar to human metabolism with hydroxylation as the primary pathway of elimination (Paulson et al., 2000b,c). Dogs are unique compared with the other species in that there is a polymorphism in the canine metabolism of celecoxib with existence of two phenotypes identified as extensive (EM) or poor (PM) metabolizers (Paulson et al., 1999).

There are numerous reviews on the effects of food on the pharmacokinetics of drugs (Karim, 1996; Welling, 1996; Fleisher et al., 1999; Singh, 1999). Food most often affects

ABBREVIATIONS: NSAID, nonsteroidal anti-inflammatory drug; COX, cyclooxygenase; EM, extensive metabolizer; PM, poor metabolizer; GI, gastrointestinal; CIAP, chronic intestinal access port; Cmax, observed peak plasma concentration; Tmax, time to peak plasma concentration; AUC, area under the plasma concentration-time curve; BA, bioavailability; IG, intragastrically.
drug absorption and metabolism. Administration of drugs with food may reduce, delay, increase, or have no effect on drug absorption. Food can affect GI physiology (gastric emptying time, acid secretion, blood flow, intestinal motility, bile secretion, and enzyme secretion), and thereby drug absorption. The potential for a food-drug interaction is dependent upon the region of the GI tract where the drug is absorbed. Drugs only absorbed in the upper intestine have a greater potential for reduced absorption when given with food (Fleisher et al., 1999).

The objective of the present study was to examine the pharmacokinetics of celecoxib after oral single and multiple dose administration. In addition, the effects of food, different dose forms and site-specific administration on celecoxib bioavailability were studied. Also, the appropriateness of the dog as a model for human celecoxib absorption was addressed.

Materials and Methods

Chemicals. Celecoxib was synthesized at G.D. Searle (Skokie, IL). Investigational celecoxib drug supplies were provided by G.D. Searle. All other reagents and solvents were of analytical grade. The neat chemical was micronized by ball-milling. Formulated capsules were composed of celecoxib sieved through an 840-μm screen and wet granulated with water-soluble diluents. The particle size for the neat chemical and formulated chemical was 5 μm.

Dogs. Male and female pure-bred beagle dogs weighing between 7 and 14 kg were used (Hazleton Research Products, Inc., Cumberland, VA; HRP, Kalamazoo, MI). Dogs were screened for population phenotype (poor or extensive metabolizer) as previously described (Paulson et al., 1999). The animals were housed unrestrained, individually in stainless steel cages, and were allowed access to food (PMI Feeds, Inc., Richmond, IN) and water ad libitum unless otherwise indicated.

Single Dose Pharmacokinetics in Dogs. Dogs (n = 12) were fasted overnight before dosing and were given access to food approximately 4 h postdose. Dogs were administered celecoxib i.v. and orally in a solution, as neat chemical capsule and formulated in a capsule in a nonrandomized, crossover design at a dose of 5 mg/kg. The i.v. and oral dose solutions were prepared in a vehicle of polyethylene glycol 400/saline (2:1, v/v) at a concentration of 5 mg/ml for the i.v. dose and a concentration of 2 mg/ml for the oral dose. The animals were dosed at approximately 8 AM. There was at least a 7-day washout period between each dose. Venous blood (approximately 3 ml) from the jugular vein was collected into chilled tubes containing sodium heparin from the animals at approximately 5, 10, 15, 30, and 45 min and 1, 1.5, 2, 2.5, 3, 3.5, 5, 6, 8, 12, 18, 24, and 48 h after the i.v. dose and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, and 24 h after the oral doses.
was also calculated by the linear trapezoidal rule. The absolute absorption of celecoxib is also faster when administered as neat chemical or formulated in a gelatin capsule. when administered as a solution compared with when the drug is administered as neat chemical or formulated in a gelatin capsule with the respective $T_{\text{max}}$ of 0.67, 1.5, and 1.3 h for EM dogs and 0.5, 3.3, and 1.3 h for PM dogs.

### Multiple Dose Studies in Dogs

The pharmacokinetic parameters of celecoxib (7.5, 12.5, and 17.5 mg/kg b.i.d.) for up to 1 year are shown in Figs. 2 and 3, respectively. The AUC values increased approximately proportional with increasing dose. The AUC values remained nearly constant over the 1-year dosing period with no consistent increase or decrease with time. The systemic exposure to celecoxib as measured by AUC or $C_{\text{max}}$ was greater in PM compared with EM dogs.

### Food Effect Study in Dogs

Figure 4 shows the plasma concentration-time profiles for celecoxib after oral administration to both fed and fasted dogs. The pharmacokinetic parameters of celecoxib in the fed and fasted state are listed in Table 3. The administration of celecoxib in the presence of food delayed absorption in all dogs except one PM animal. This animal exhibited a “double peak” plasma concentration curve. The first peak occurred at 3 h and the second peak, the $C_{\text{max}}$, occurred at 18 h. The mean $T_{\text{max}}$ without this animal was 2.3 h.

### Food Effect Study in Healthy Subjects

Figure 5 shows the plasma concentration-time profiles for celecoxib after oral administration of a 200-mg celecoxib capsule to healthy subjects under fasting conditions and immediately after a high-fat breakfast. The pharmacokinetic parameters of celecoxib are listed in Table 4. The consumption of dietary fat before dosing with 200-mg celecoxib capsules increased $T_{\text{max}}$ and $C_{\text{max}}$ values 140% compared with the values obtained after dosing to the same subjects under fasting conditions. The relative bioavailability of celecoxib following administration of a 200-mg celecoxib capsule following a high-fat breakfast was 110% compared with administration of the drug under fasting conditions. Based on the ratios and the 95% confi-

### Results

#### Intravenous and Oral Single Dose Studies in Dogs

The plasma pharmacokinetic parameters after single i.v. or oral administration of celecoxib to EM or PM dogs are listed in Tables 1 and 2. After i.v. administration, the celecoxib AUC$_{0-\infty}$ is greater, $t_{1/2}$ is longer and clearance is lower in PM versus EM dogs. Celecoxib is well absorbed when administered as a solution with absolute bioavailability (BA) of 63.7 and 88.2% in EM and PM dogs, respectively. The absolute bioavailability of celecoxib is 3- to 4-fold greater when administered as a solution compared with when the drug is administered as neat chemical or formulated in a gelatin capsule. The absorption of celecoxib is also faster when administered as a solution compared with when the drug is administered as neat chemical or formulated in a gelatin capsule with the respective $T_{\text{max}}$ of 0.67, 1.5, and 1.3 h for EM dogs and 0.5, 3.3, and 1.3 h for PM dogs.

#### Food Effect Study in Dogs

Figure 4 shows the plasma concentration-time profiles for celecoxib after oral administration to both fed and fasted dogs. The pharmacokinetic parameters of celecoxib in the fed and fasted state are listed in Table 3. The administration of celecoxib in the presence of food resulted in a 3- to 5-fold increase in the extent of absorption of drug as measured by changes in $C_{\text{max}}$ and AUC$_{0-\infty}$. The administration of celecoxib in presence of food delayed absorption in all dogs except one PM animal. This animal exhibited a “double peak” plasma concentration curve. The first peak occurred at 3 h and the second peak, the $C_{\text{max}}$, occurred at 18 h. The mean $T_{\text{max}}$ without this animal was 2.3 h.

#### Food Effect Study in Healthy Subjects

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Fig. 2. Mean ± S.E.M. of AUC₀⁻²₄ of celecoxib in EM and PM dogs dosed orally at 7.5 mg/kg (b.i.d.), 12.5 mg/kg (b.i.d.), and 17.5 mg/kg (b.i.d.) for 1 year. The open columns are results from a 13-week study and the closed columns are results from a separate 1-year study.

Fig. 3. Mean ± S.E.M. of Cₘₐₓ of celecoxib in EM and PM dogs dosed orally at 7.5 mg/kg (b.i.d.), 12.5 mg/kg (b.i.d.), and 17.5 mg/kg (b.i.d.) for 1 year. The open columns are results from a 13-week study and the closed bars are results from a separate 1-year study.


dence intervals, the differences between the mean $T_{\text{max}}$, $C_{\text{max}}$, and AUC$_{0-\infty}$ values obtained under fed or fasting conditions were significant at the 5% level.

**Site of Absorption Study in Dogs.** Figure 6 shows the plasma concentration-time profiles for celecoxib after oral administration IG or through a CIAP into the duodenum, jejunum, or colon. The pharmacokinetic parameters are in Table 5. The extent of celecoxib absorption was similar following dosing to all four sites (oral, duodenum, jejunum, colon). However, the rate of celecoxib absorption was slower following administration into the colon compared with oral dosing and dosing through CIAP into the duodenum or jejunum.

**Discussion**

The dog is used extensively to evaluate oral absorption of candidate pharmaceuticals and to facilitate dosage form de-

**TABLE 3**

Mean ± S.E.M. pharmacokinetic parameters for celecoxib following a single oral dose of celecoxib (5 mg/kg as neat chemical in a gelatin capsule) to dogs that were fasted or fed a low-, medium-, or high-fat diet.

<table>
<thead>
<tr>
<th>Diet</th>
<th>No. of Dogs</th>
<th>$T_{\text{max}}$</th>
<th>$C_{\text{max}}$</th>
<th>AUC$_{0-\infty}$</th>
<th>Absolute BA %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$h$</td>
<td>$\mu g/ml$</td>
<td>($\mu g/mlh$)</td>
</tr>
<tr>
<td>EM dogs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasted</td>
<td>3</td>
<td>1.5 ± 0.3</td>
<td>0.23 ± 0.04</td>
<td>1.7 ± 0.7</td>
<td>27.4 ± 14.6</td>
</tr>
<tr>
<td>Low fat</td>
<td>3</td>
<td>3.0 ± 0.5</td>
<td>0.67 ± 0.23</td>
<td>4.1 ± 1.5</td>
<td>59.9 ± 16.1</td>
</tr>
<tr>
<td>Medium fat</td>
<td>3</td>
<td>5.3 ± 0.7</td>
<td>0.58 ± 0.14</td>
<td>4.1 ± 1.2</td>
<td>60.4 ± 11.8</td>
</tr>
<tr>
<td>High fat</td>
<td>3</td>
<td>4.0 ± 1.2</td>
<td>0.66 ± 0.11</td>
<td>5.0 ± 1.4</td>
<td>74.4 ± 12.1</td>
</tr>
<tr>
<td>PM dogs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasted</td>
<td>3</td>
<td>7.5 ± 5.3a</td>
<td>0.49 ± 0.10</td>
<td>3.9 ± 0.4</td>
<td>42.2 ± 4.9</td>
</tr>
<tr>
<td>Low fat</td>
<td>3</td>
<td>3.8 ± 1.1</td>
<td>0.89 ± 0.05</td>
<td>8.1 ± 0.7</td>
<td>87.5 ± 9.2</td>
</tr>
<tr>
<td>Medium fat</td>
<td>3</td>
<td>4.7 ± 0.7</td>
<td>0.76 ± 0.05</td>
<td>6.3 ± 0.3</td>
<td>67.9 ± 2.6</td>
</tr>
<tr>
<td>High fat</td>
<td>3</td>
<td>7.3 ± 0.7</td>
<td>0.89 ± 0.03</td>
<td>8.8 ± 0.5</td>
<td>93.7 ± 1.1</td>
</tr>
</tbody>
</table>

* Mean $T_{\text{max}}$ without the animal that exhibited a “double peak” plasma concentration curve was 2.3 h.
velopment. In the present report, the dog was used to study the absorption of celecoxib administered in solution and as a solid, following single and multiple dosing, with and without food, and after administration into different sites of the GI tract.

There is a marked difference in the pharmacokinetic profile for celecoxib when the drug is given orally in solution compared with when it is administered as a solid to dogs. Celecoxib was rapidly absorbed when given orally as a solution with a $T_{\text{max}}$ of less than 1 h. The $T_{\text{max}}$ for celecoxib was prolonged for another 1 to 2 h when given as a solid. The slower absorption of celecoxib from solid dosage forms was likely due to the time necessary for dispersion and dissolution of celecoxib in the milieu of the GI tract. Celecoxib was well absorbed when given in a solution with an absolute BA of 63.7% for EM dogs and 88.2% for PM dogs. The absolute BA of celecoxib was significantly lower when the drug was given as a solid (21.7% for EM dogs and 39.4% for PM dogs). The near complete absorption of celecoxib from the solution and an octanol/water partition coefficient of greater than $1 \times 10^3$ support that celecoxib is a highly permeable drug. The limited absorption of celecoxib as a solid is indicative of a poorly soluble drug with bioavailability that is dissolution rate limited. The aqueous solubility of celecoxib is low at 3 to 7 $\mu$g/ml when determined in vitro at pH 7 and 40°C. Since the $pK_a$ of celecoxib is 11.1 the solubility of the drug is likely to also be low at physiological pH. The lower systemic availability in EM dogs is likely a reflection of greater first pass metabolism than in the PM animal.

The regional difference in intestinal absorption of celecoxib was evaluated in conscious dogs using chronic intestinal access ports (Meunier et al., 1993). The properties of the intestine differ throughout its length. The surface area available for absorption is greatest in duodenum with the presence of the microvilli and lowest in the colon. Transit time is 3 to 4 h in the small intestine and can be up to 24 h in the colon (Davies and Morris, 1993). The observations that the systemic exposure to celecoxib given IG was the same following direct administration into the duodenum, jejunum, and colon support that celecoxib is a highly permeable drug that can be absorbed through the GI tract.

Food had a remarkable effect upon the absorption profile of celecoxib in the dog. Although $T_{\text{max}}$ was delayed by food, the absolute BA of celecoxib was increased about 3-fold following administration as a solid to the fed compared with fasted animal. In fact, absolute BA of celecoxib when given with food approached the absolute BA of celecoxib when given as a solution. These data suggest that the effect of food is to enhance the dissolution of celecoxib. The consumption of a meal can have many effects upon the GI physiology that influence drug absorption, especially those compounds that are highly lipophilic (Karim, 1996). Food is known to change gastric motility to a postprandial pattern and to delay gastric emptying (Welling, 1996; Fleisher et al., 1999). Although these changes would likely result in delayed drug absorption due to delayed gastric emptying, the longer gastric residence time would allow more time for dispersion and dissolution of a poorly soluble, lipophilic drug such as celecoxib thereby increasing the extent of absorption. The secretion of bile salts and the larger volume of gastric fluid after a meal may also increase the dissolution rate of poorly soluble drugs. Cyclosporin and griseofulvin are lipophilic drugs whose absorption

![Fig. 5. Mean ± S.D. plasma concentrations of celecoxib in healthy adults administered a single 200-mg celecoxib capsule under fasting conditions or after a high-fat breakfast in a randomized, crossover design study.](image)

| Table 4 | Mean ± S.D. pharmacokinetic parameters for celecoxib following administration of a single oral dose of celecoxib capsule (200 mg) to healthy subjects under fasting conditions or immediately after a high-fat breakfast in a randomized, crossover study |
| --- | --- | --- | --- | --- | --- |
| Treatment | No. of Subjects | $T_{\text{max}}$ (h) | $C_{\text{max}}$ (ng/ml) | AUC$_{0-48}$ (ng/ml*h) | AUC$_{0-\infty}$ (ng/ml*h) | Relative BA |
| Fasted | 24 | 2.44 ± 0.83 | 806 ± 411 | 5994 ± 2393 | 6564 ± 2383 | 110.7 |
| High-fat breakfast | 24 | 3.42 ± 1.28 | 1042 ± 355 | 7141 ± 2887 | 7318 ± 2818 | 110.7 |

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is enhanced by bile salts (Lindholm et al., 1990; Charman et al., 1997). Unlike dog, a high-fat diet had minimal effect on the extent of celecoxib absorption in humans. The systemic exposure to celecoxib as measured by $AUC_{0-\infty}$ and $C_{\text{max}}$ was increased only 10.7 and 25%, respectively, when the drug was given with a high-fat breakfast to healthy subjects. This increase in systemic exposure to celecoxib following administration with food is not clinically relevant. The consumption of a high-fat breakfast also delayed celecoxib absorption in humans resulting in $T_{\text{max}}$ values that were 2 to 3 h more prolonged compared with $T_{\text{max}}$ values obtained under fasting state; most likely a result of delayed gastric emptying.

The food effects studies in the dogs and humans were conducted under different conditions that could have contributed to the differences in the magnitude of the absorption response to food. The healthy subjects received a 200-mg dose (2.85 mg/kg for a 70-kg body weight) and the dogs received 5 mg/kg (35–70 mg depending on body weight). The dogs were given the celecoxib as neat chemical and the healthy subjects were administered a formulated capsule. However, there was no difference in the bioavailability of celecoxib following administration as neat chemical or in a formulated capsule to EM dogs.

Although the dog is a useful and convenient model for humans there are differences between the two species that may affect an oral pharmacokinetic profile. Under fasting conditions, the gastric emptying time is similar between the two species but the intestinal transit time is twice as long in the human as dog (Dressman, 1986). In humans, the longer intestinal transient time coupled with the ability of celecoxib to be absorbed throughout the GI tract may allow for a complete absorption of the compound under fasting conditions and a minimal change in absorption with food. Whereas, in dogs, a shorter intestinal transient time under fasting conditions would allow less time for dissolution, resulting in incomplete absorption. Consumption of a meal will delay gastric emptying in both species. Compared with humans, the dog has a slower gastric emptying time after feeding (Meyer et al., 1985). The longer gastric residence time, in dogs, after a meal may allow more time for dissolution, resulting in the marked increased in the extent of absorption of celecoxib. Further investigation is needed to fully understand this species difference in food on the absorption of celecoxib.

Celecoxib absorption did not change after multiple dose administration. Systemic exposure to celecoxib in dogs remained constant following daily administration of the drug for up to 1 year.

In conclusion, celecoxib is a poorly soluble, highly permeable drug, i.e., class 2 of the Biopharmaceutical classification

**Table 5**

Mean ± S.E.M. pharmacokinetic parameters for celecoxib after administration of celecoxib (10 mg/kg in a solution) IG or directly through a chronic intestinal access port into the duodenum, jejunum, or colon of beagle dogs.

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of Dogs</th>
<th>$T_{\text{max}}$</th>
<th>$C_{\text{max}}$</th>
<th>$AUC_{0-24}$</th>
<th>$AUC_{0-\infty}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(h)</td>
<td>(\mu g/ml)</td>
<td>(\mu g/ml)</td>
<td>(\mu g/ml)</td>
<td>(\mu g/ml)</td>
</tr>
<tr>
<td>IG</td>
<td>4</td>
<td>0.69 ± 0.28</td>
<td>1.62 ± 0.36</td>
<td>10.3 ± 2.0</td>
<td>11.3 ± 2.2</td>
</tr>
<tr>
<td>Duodenum</td>
<td>4</td>
<td>1.13 ± 0.63</td>
<td>1.46 ± 0.29</td>
<td>9.69 ± 1.57</td>
<td>10.1 ± 1.5</td>
</tr>
<tr>
<td>Jejunum</td>
<td>4</td>
<td>2.25 ± 1.92</td>
<td>1.06 ± 0.21</td>
<td>9.37 ± 0.97</td>
<td>12.1 ± 2.2</td>
</tr>
<tr>
<td>Colon</td>
<td>4</td>
<td>8.5 ± 2.0</td>
<td>0.79 ± 0.12</td>
<td>10.0 ± 0.9</td>
<td>10.8 ± 1.0</td>
</tr>
</tbody>
</table>

**Fig. 6.** Individual plasma concentrations of celecoxib in beagle dogs administered 10 mg/kg with celecoxib IG or through a CIAP into the duodenum, jejunum, or colon.
system. The absorption of celecoxib is minimally affected when administered with food in humans. Therefore, for chronic administration patients with arthritis can be given celecoxib with or without food. For acute therapy; however, celecoxib may be preferably given under fasting state to avoid the food-induced lag time in its absorption.

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References


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