DISPOSITION OF L-738,167, A POTENT AND LONG-ACTING FIBRINOGEN RECEPTOR ANTAGONIST, IN DOGS

Dose-Dependent Pharmacokinetics

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ABSTRACT:

L-738,167 is a potent and long-acting fibrinogen receptor antagonist and may be useful for treatment of chronic thrombotic occlusive disorders. The purposes of this study were to characterize the metabolism and disposition of L-738,167, and to investigate factors affecting its pharmacokinetic behaviors in dogs, one of the animal models used in pharmacological and toxicological studies. In vitro and in vivo experiments indicated that L-738,167 was not metabolized to any appreciable extent in dogs. Biliary excretion was found to be the major route (~75%) of drug elimination. Following 1 and 3 μg/kg iv doses, blood pharmacokinetics of L-738,167 were linear. Total blood clearance (CLB) was much lower than hepatic blood flow, and the apparent volume of distribution at steady-state (Vdss,B) was comparable with blood volume. Blood pharmacokinetics in the dose range of 3–250 μg/kg were dose-dependent; both CLB and Vdss,B for L-738,167 increased markedly with increasing doses. However, the terminal half-life (t1/2) was dose-independent, with a mean value of ~4 days. L-738,167 was found to bind negligibly to dog plasma proteins. Determinations of whole blood (WB), platelet-rich plasma, and platelet-poor plasma concentrations after several intravenous doses of [3H]L-738,167 revealed significant concentration-dependent binding of the compound to platelets. Kinetic analysis of the platelet binding indicated that L-738,167 was bound to dog platelets with high affinity (apparent Kd ~ 1 nM platelet-poor plasma concentration) and relatively low capacity (~70 nM WB concentration). Findings are consistent with the binding kinetics of L-738,167 to glycoprotein IIb/IIIa (GP IIb/IIIa) receptor, supporting that GP IIb/IIIa was the primary binding component on the platelets. It was concluded that the dose-dependent pharmacokinetics of L-738,167 were the consequence of the concentration-dependent drug-platelet binding. Due to this extensive platelet binding, L-738,167, when given in therapeutic doses or lower, resided primarily in the vascular compartment—the site of pharmacological action. At doses exceeding the receptor binding capacity, the excess amount or the unbound drug was eliminated rapidly. In all cases, the equally long t1/2 of L-738,167 was also a consequence of the high-affinity binding to platelets, in good agreement with its prolonged pharmacodynamic profile.

GP IIb/IIIa receptor, a member of the integrin superfamily of the membrane-bound adhesive molecules, is the most abundant platelet cell-surface protein (1). Binding of fibrinogen to activated platelets has been shown to be mediated completely by GP IIb/IIIa (2). This binding is essential and is the final common pathway for platelet aggregation by all agonists (2). Thus, compounds capable of blocking this binding could theoretically be useful in preventing thrombus formation. The first specific GP IIb/IIIa antagonist, the monoclonal antibody 7E3, has been shown to inhibit effectively platelet aggregation against all known platelet agonists in experimental animals and patients (3, 4). Because GP IIb/IIIa has a high affinity for RGD, which is found in several adhesive proteins (1, 2), several RGD analogs and nonpeptide RGD mimetics have also been developed as active inhibitors of platelet GP IIb/IIIa-fibrinogen interaction (5–8). Some of these compounds are being tested clinically for the treatment of vascular occlusive disorders (9–13).

L-738,167 (fig. 1) is a potent nonpeptide antagonist of platelet GP IIb/IIIa-fibrinogen interaction (5–8). Some of these compounds are being tested clinically for the treatment of vascular occlusive disorders (9–13).

Materials and Methods

Chemicals. L-738,167, 2(S)-[(p-toluenesulfonyl)amino]-3-[(5,6,7,8-tetrahydro-4-oxo-5-[2(piperidin-4-yl)ethyl]-4H-pyrazolo[1,5-a][1,4]diazepin-2-yl]carbonylaminopropionic acid, and [3H]-L-738,167 (fig. 1) were synthesized at Merck Research Laboratories (West Point, PA) as described (14). The
labeled material had a radioactive purity of >98%, as determined by HPLC, and was diluted with the appropriate amounts of carrier drug. NADPH and UDPGA were obtained from Sigma Chemical Co. (St. Louis, MO). Solvents used for HPLC analysis were of analytical or HPLC grade.

**Animals.** Male beagle dogs (9–13 kg) were used in cross-over design studies. A washout period of 2–4 weeks (a minimum of 3 weeks before the studies at doses of 1 and 3 μg/kg) was used between studies. Animals were deprived of food for ~18 hr before dosing, and were housed in individual metabolism cages for urine and feces collection.

**In Vivo Study.** [3H]-L-738,167 (in saline) was administered to male beagle dogs (N = 3–4) intravenously at doses of 1, 3, 25, and 250 μg/kg. WB was collected at appropriate time intervals for up to 1 week. An aliquot of WB was kept frozen for analysis of total radioactivity (see Analytical Procedure), and the remaining sample was centrifuged at a low speed (150g) for ~7 min to obtain PRP. After harvesting PRP, the sample was further centrifuged at 2000 g for 10 min to yield PPP. WB, PRP, and PPP samples obtained from all studies were analyzed for total radioactivity. At a 1 μg/kg dose, only WB samples were collected and analyzed. Platelet counts in WB, PRP, and PPP samples were monitored (every study day for WB, and most sampling times for PRP and PPP) using a cell counter (Serona Baker Diagnostics System 9000, Allentown, PA). The numbers of platelets in these dogs ranged between 220–350 x 10^3/μl in WB. Only PRP samples with platelet counts within ±25% of the mean values obtained for each dog at each study dose and PPP samples with platelet counts of ±5 x 10^3/μl were included in the data analysis.

Urine and feces were collected up to 14 days after dosing. Radioactivity was measured to determine overall recovery of the dose. Metabolite profiling of these samples was performed using a radiochromatographic method described in Analytical Procedure.

**In Vitro Study.** In Vitro Metabolism. Dog liver S9 fractions (3 mg/ml) or liver microsomes (2 mg/ml) were incubated with [3H]-L-738,167 (~0.1 μCi) and NADPH (1 mM) in phosphate buffer (pH 7.4). After a 60-min incubation at 37°C, the reaction was stopped with 5 ml methanol. The methanol extract was evaporated, reconstituted with an HPLC mobile phase, and analyzed using the radiochromatographic method described herein. Incubations were also conducted, in the absence and presence of Triton X-100 (0.2%), using UDPGA (3 mM) as an enzyme cofactor.

**Plasma Protein Binding.** An ultrafiltration method was used to estimate drug-plasma protein binding. The in vitro study was performed in triplicate using PPP samples from untreated dogs, adjusted to pH 7.4, at [3H]-L-738,167 final concentrations of 4–500 nM. Samples were incubated at 37°C for 15 min and transferred to a Centrifree unit (Amicon Co., Danver, MA). Tubes were centrifuged at 37°C for 20–30 min. Unbound fractions were estimated directly for drug radioactivity in the plasma filtrate and the starting plasma radioactivity. Preliminary experiments indicated negligible binding of the drug to the ultrafiltrate device. Plasma protein binding was also determined ex vivo using PPP samples obtained from the previously described in vivo studies.

**Analytical Procedure.** Radioactivity Measurement. WB was combusted using a Packard model 306 oxidizer and analyzed for total radioactivity. Total radioactivity in PRP and PPP samples was measured directly using a scintillation counter (Packard model 1500), or was determined after combustion as for WB. Preliminary studies indicated minimal loss of 3H in plasma samples to water. Urine and cage wash were measured directly for total radioactivity. Feces were homogenized in water and were combusted and analyzed for total radioactivity.

**Radiochromatographic Method.** Aliquots of urine samples (0.1–0.2 ml) were chromatographed directly onto the column. Fecal homogenates (1 ml) were extracted with 5 volumes of methanol, evaporated to dryness, reconstituted with mobile phase, and subjected to HPLC analysis. Chromatography was performed on a Spherisorb C18 column (3.9 x 300 mm, 5 μm) eluted at a flow rate of 1 ml/min with a linear gradient (1%/min) of 0–30% acetonitrile (A) in 10 mM ammonium acetate containing 0.1% trifluoroacetic acid (B), followed by a 10-min isocratic elution step (90% A in B). The eluate was monitored at 240 nm and by an on-line radioactivity detector (Ramona-5-LS).

**Data Analysis.** Pharmacokinetic Analysis. Because metabolism of L-738,167 was found to be negligible (see Results), pharmacokinetic parameters were estimated using total radioactivity in WB as L-738,167 blood concentration. CLq’s were estimated by dividing intravenous doses with AUCs from time 0 to infinity. Vd,α,β was calculated using a noncompartmental model (17).

**Kinetic Analysis of Platelet Binding.** Nonlinear regression analysis (PC-NONLIN, Statistical Consultant, Lexington, KY) was used to estimate the apparent dissociation constant of platelet binding, Kd and the capacity constant, based on the following relationship:

\[ C_{total} = C_{free} + [(Capacity constant/(K_d + C_{total})) + 1]. \]

where, Cfree and Ctotal were the concentrations of free drug and total drug (free and platelet bound), respectively. The total radioactivity in PPP represented Cfree because the plasma protein binding of L-738,167 was found to be negligible in dogs (see Results). Considering that PRP consisted largely of platelets and PPP, the total radioactivity in PRP represented Ctotal. Consequently, the resulting values were expressed as PPP concentrations for the apparent Kd and PRP concentrations for the capacity constant.

**Results**

**In Vivo Study.** Table 1 shows the excretion profile of [3H]-L-738,167 at the intravenous doses of 3, 25, and 250 μg/kg. Total recovery during 4 days was only ~50% after the 3 μg/kg dose, whereas it was virtually complete after the higher doses. For the dose of 3 μg/kg, complete recovery was obtained after ~3 weeks postdose (data not shown). In the dose range of 25–250 μg/kg, >80% of the total radioactivity was recovered in the excreta during the 0- to 24-hr period, and ~<5% of the dose was recovered during 48–96 hr. The bile–urine excretion ratio of [3H]-L-738,167 seemed consistent over the dose range studied; biliary excretion was the major elimination pathway, accounting for about two-thirds of the total (table 1).

**TABLE 1**

<table>
<thead>
<tr>
<th>Dose (μg/kg)</th>
<th>N</th>
<th>Urine (Ci)</th>
<th>0–24 Hr</th>
<th>Total</th>
<th>Urine (Ci)</th>
<th>0–96 Hr</th>
<th>Total</th>
</tr>
</thead>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0–24 Hr</td>
<td>Total</td>
<td></td>
<td>0–96 Hr</td>
<td>Total</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>6.3 ± 2.7</td>
<td>17.3 ± 1.4</td>
<td>23.4 ± 3.2</td>
<td>11.2 ± 3.5</td>
<td>38.1 ± 0.5</td>
<td>49.4 ± 3.9</td>
</tr>
<tr>
<td>25</td>
<td>4</td>
<td>23.9 ± 7.8</td>
<td>59.2 ± 9.6</td>
<td>83.1 ± 15.8</td>
<td>26.4 ± 7.9</td>
<td>75.8 ± 9.0</td>
<td>102.2 ± 13.4</td>
</tr>
<tr>
<td>250</td>
<td>4</td>
<td>24.8 ± 6.5</td>
<td>64.2 ± 7.8</td>
<td>89.1 ± 11.0</td>
<td>25.8 ± 5.2</td>
<td>78.4 ± 6.5</td>
<td>103.7 ± 8.2</td>
</tr>
</tbody>
</table>

* Including cage wash.
Metabolite profiling of urine and feces revealed that the majority (>95%) of the total radioactivity was the parent drug, indicating that metabolism of L-738,167 in dogs was minimal.

Blood radioactivity-time profiles obtained after intravenous administration of [3H]L-738,167 to dogs in the dose range of 1–250 μg/kg are depicted in fig. 2. At doses of 1 and 3 μg/kg, blood levels obtained over all sampling times appeared proportional to the doses. In the dose range of 3–250 μg/kg, blood levels were markedly different among doses at early time points. However, after 6–8 hr of dosing, they appeared parallel and comparable (~2-fold differences), despite ~80-fold increases in dose. As shown in table 2, kinetics of L-738,167 were linear at doses of 1 and 3 μg/kg. CL_B and Vd_ss,B were low, relative to hepatic blood flow and body water, respectively. At doses >3 μg/kg, nonlinear pharmacokinetics were apparent; both CL_B and Vd_ss,B increased with increases in dose. The t_1/2 was estimated to be ~4 days and was dose-independent.

At the 3 μg/kg dose, total radioactivity in WB, PRP, and PPP declined slowly and seemed parallel to each other (fig. 3A). At the higher dose (25 μg/kg), total radioactivity in PRP still declined in parallel with that in WB, reaching near plateau levels of ~10–20 ng/ml within a few hours after dosing (fig. 3B). However, radioactivity in PPP declined rapidly and then, at much lower levels (<2 ng/ml), slowly declined in parallel to the total radioactivity in WB and PRP. For all doses, the WB/PRP concentration ratios were relatively constant, ranging from 0.5 to 0.9, with a mean value of ~0.7 (fig. 4). Concentration-dependent binding of L-738,167 to blood components was apparent; concentrations in PPP were close to those in WB or PRP at high concentrations, but significantly less (up to 65-fold) at lower concentrations (fig. 4). Due to an apparent ill-defined terminal phase, resulting from very low radioactivity levels and possible contamination of microvascular particles in PPP samples, pharmacokinetic parameters using PPP data were not obtained.

Figure 5 depicts the relationship between total radioactivity in PRP or radioactivity associated with platelets (obtained directly by subtracting concentrations in PPP from those in PRP) and the total radioactivity in PPP after administration of [3H]L-738,167 in dogs. Evidently, platelet binding was dependent on L-738,167 concentrations, with the apparent saturation level of ~60 ng/ml (PRP concentration).

Analysis of platelet binding kinetics revealed a very high affinity, but low-capacity binding of L-738,167 to dog platelets. The apparent K_d value estimated in terms of PPP concentration was 0.7 ng/ml or 1.2 nM, and the capacity constant value calculated as PRP concentration was ~60 ng/ml or 100 nM (table 3). Based on the average WB/PRP concentration ratio of ~0.7, the capacity constant expressed in term of WB concentration was equivalent to ~70 nM.

**In Vitro Study. In Vitro Metabolism.** L-738,167 was resistant to metabolism by dog liver microsomes or S_9 fractions in the presence of...
NADPH or UDPGA. Results are consistent with the conclusion of insignificant metabolism obtained in vivo.

**Plasma Protein Binding Study.** Negligible binding (<15%) to dog plasma protein was observed in vitro or ex vivo, over the concentration range studied.

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**Discussion**

The present study investigated the metabolism, disposition kinetics, and platelet binding kinetics of L-738,167. Both the in vivo and in vitro experiments demonstrated that L-738,167 was a metabolically...
stable compound. In the in vivo experiments, results were further confirmed by comparable values of the radioactivity levels in PRP and L-738,167 PRP concentrations determined using the specific and sensitive LC/MS/MS assay (data not shown). In our experience, several polar and zwitterionic compounds in this class were found to undergo little metabolism, especially in dogs (18–20). Because L-738,167 was found to be not well absorbed orally (<10%, data not shown), the total radioactivity recovered in feces was a close approximation of the total amount excreted into bile. The finding that biliary excretion was the major elimination pathway (table 1) is consistent with high molecular weight (molecular weight = 547) of the compound (21).

L-738,167 could be characterized in dogs as a low clearance compound. Its pharmacokinetics were dose-dependent. For a low clearance compound, the dose-dependency of CL₂ suggests possible non-linearity of drug binding to blood components (22). In the case of L-738,167, plasma protein was ruled out as the major binding protein, because the binding was not extensive, and it was independent of L-738,167 concentrations. Considering that PRP contains negligible red blood cells, and that the hematocrit value was ~45%, the mean WB/PRP radioactivity ratios of ~0.7 obtained in the present study suggested also that red blood cells were not the primary binding component for L-738,167. The finding of PRP/PPP concentration ratios of up to 65 strongly indicated that L-738,167 was bound extensively to dog platelets. The binding of L-738,167 to platelets exhibited concentration dependence and, kinetically, could be characterized as very high-affinity and low-capacity binding. The apparent \( K_a \) value of 1 nM obtained in the present study was comparable with that obtained with purified GP IIb/IIIa (14, 15). The binding capacity constant of ~100 nM PRP or 70 nM WB also agrees with the estimated GP IIb/IIIa WB concentrations of ~50 nM, calculated based on 100 GP IIb/IIIa molecules/platelet and 300 \( \times 10^3 \) platelets/\( \mu \)l WB (15, 23). The present results suggest that GP IIb/IIIa was the major binding protein on the dog platelets and agree with earlier findings that L-738,167 is a potent GP IIb/IIIa antagonist (14, 15).

The high-affinity, but low-capacity binding characteristics of L-738,167 greatly influenced its pharmacokinetic behaviors. The dose-dependence in \( CL_B \) was consistent with the concentration-dependent WB/PPP or PRP/PPP, arising from saturation of L-738,167 binding to platelets. At the low blood concentrations (<35 ng/ml or 70 nM) that were obtained after the 1 and 3 \( \mu \)g/kg doses, L-738,167 was bound linearly to platelets, with a constant free fraction in plasma available for elimination. Due to high-affinity binding, only a small fraction was free for subsequent elimination, resulting in low \( CL_B \). However, at concentrations exceeding the binding capacity (>70 nM WB), as was the case after the higher doses, free fraction was greatly increased. As a consequence, \( CL_B \) increased because the rate of elimination is dependent on the free fraction for low hepatic extraction compounds (22).

The \( V_d \) value of ~0.15 liters/kg obtained at the lower doses was comparable with blood volume in dogs (24), indicating that the compound resided primarily in the vascular compartment (25). This also is consistent with the high-affinity binding of L-738,167 to platelets. As L-738,167 doses increased, the binding site was saturated, resulting in more free fraction available for distribution to other sites; consequently, the \( V_d \) increased (25). However, because the \( V_d \) was estimated based on an assumption of linear kinetics, this change in \( V_d \) obtained might not accurately reflect the change in its tissue distribution (17).

The \( t_{1/2} \) was independent of doses because it reflected the concentration-time profile during the linear kinetics of drug-platelet binding (<70 nM WB; fig. 2). The long half-life agreed with the drug prolonged duration of action. Despite the long half-life, >80% of the total radioactivity was recovered during the 0- to 24-hr period after the saturating doses (25 and 250 \( \mu \)g/kg) (table 1). This finding did not correlate with ~20% of the total AUC from WB or PRP levels obtained during the same time period. Results suggest that L-738,167,

**TABLE 3**

*Kinetic parameters of t-738,167-platelet binding*

Results were obtained after intravenous administration of \([\text{H}]_{t-738,167}\) (3, 25, and 250 \( \mu \)g/kg) to dogs (see Materials and Methods).

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>( K_d )</th>
<th>Capacity Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ng/ml</td>
<td>ng/ml</td>
</tr>
<tr>
<td>1</td>
<td>0.65</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>NA*</td>
<td>NA*</td>
</tr>
<tr>
<td>3</td>
<td>0.43</td>
<td>59</td>
</tr>
<tr>
<td>4</td>
<td>0.96</td>
<td>63</td>
</tr>
<tr>
<td>Mean</td>
<td>0.68</td>
<td>59</td>
</tr>
<tr>
<td>SD</td>
<td>0.27</td>
<td>4</td>
</tr>
</tbody>
</table>

*NA*, not available due to insufficient data.

\( K_d \) value of 1 nM obtained in the present study was comparable with that obtained with purified GP IIb/IIIa (14, 15). The binding capacity constant of ~100 nM PRP or 70 nM WB also agrees with the estimated GP IIb/IIIa WB concentrations of ~50 nM, calculated based on 100 GP IIb/IIIa molecules/platelet and 300 \( \times 10^3 \) platelets/\( \mu \)l WB (15, 23). The present results suggest that GP IIb/IIIa was the major binding protein on the dog platelets and agree with earlier findings that L-738,167 is a potent GP IIb/IIIa antagonist (14, 15).

The high-affinity, but low-capacity binding characteristics of L-738,167 greatly influenced its pharmacokinetic behaviors. The dose-dependence in \( CL_B \) was consistent with the concentration-dependent WB/PPP or PRP/PPP, arising from saturation of L-738,167 binding to platelets. At the low blood concentrations (<35 ng/ml or 70 nM) that were obtained after the 1 and 3 \( \mu \)g/kg doses, L-738,167 was bound linearly to platelets, with a constant free fraction in plasma available for elimination. Due to high-affinity binding, only a small fraction was free for subsequent elimination, resulting in low \( CL_B \). However, at concentrations exceeding the binding capacity (>70 nM WB), as was the case after the higher doses, free fraction was greatly increased. As a consequence, \( CL_B \) increased because the rate of elimination is dependent on the free fraction for low hepatic extraction compounds (22).

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when administered in excess amount, was eliminated rapidly until it reached the platelet binding capacity. The remaining amount, representing only a minor fraction of the administered doses, was mainly associated with platelets, the pharmacological site. This conclusion was supported by the finding of comparable blood levels obtained after 6–8 hr of dosing over the dose range of 3–250 μg/kg (fig. 2). Under this condition (linear kinetics), only a very small free fraction of L-738,167 was available for elimination, with a t½ value of ~4 days. That is, the total radioactivity recovered in the excreta would correlate well with AUC obtained from WB during the corresponding time period, and ~50% of the administered dose would be eliminated in 4 days. This conclusion was again supported by the findings that the total radioactivity recovered in the excreta and the AUC obtained from WB during the 4-day postdose period after the 3 μg/kg dose was ~50% (table 1 and data not shown).

The present study illustrated another example of dose-dependent kinetics of a compound due to saturation of intravascular binding sites other than plasma proteins. Similar observations have been reported with the binding of carbonic anhydrase inhibitors to the carbonic anhydrase enzymes in red blood cells (26, 27). However, due to much higher affinity and lower capacity of the platelet binding, the dose-dependent kinetics of L-738,167 were observed at much lower doses. Based on comparable kinetic parameters of L-738,167 platelet binding obtained using human PRP and dog PRP (preliminary data), the pharmacokinetic behaviors of L-738,167 in humans may resemble those observed in dogs.

To conclude, L-738,167 was characterized in dogs as a metabolically stable, low-clearance, and low volume of distribution compound, with biliary excretion as the major route of elimination. L-738,167 was not bound to plasma proteins, but was bound extensively to dog platelets, most likely to GP IIb/IIIa, with high affinity but low capacity. Furthermore, at lower doses, the amount exceeding the receptor binding capacity would be eliminated rapidly. Subsequently, WB levels of L-738,167 after any given higher doses would not be much higher than the capacity (~70 nM) of L-738,167 platelet binding, with the exception of the levels during the initial phase. L-738,167 exhibited a long half-life of ~4 days, a consequence of its high-affinity platelet binding property, agreeing with the compound’s prolonged action. This long half-life feature of L-738,167 may enable the use of a once-a-day dosing regimen.

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References


