Pharmacokinetics and Pharmacodynamics of an Investigational Antipsychotic Agent, CI-1007, in Rats and Monkeys

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Received November 23, 1996; accepted December 18, 1996

Purpose. To study the pharmacokinetics (PK) and pharmacodynamics (PD) of an investigational antipsychotic agent, CI-1007, in rats and monkeys.

Methods. CI-1007 and a pharmacologically active metabolite, PD 147693 (M1), were evaluated in animal antipsychotic tests (inhibition of dopamine neuron firing and spontaneous locomotor activity in rats, and inhibition of continuous avoidance in monkeys). Plasma concentrations of CI-1007 and M1 were determined using validated HPLC assays. Log-linear and link models were used for PK/PD analysis.

Results. CI-1007 and M1 have shown similar effects on dopamine neuron firing (2.5 mg/kg i.p.), and produced dose-related effects on spontaneous locomotor activity in rats (0.3–30 mg/kg, p.o.) and on continuous avoidance in monkeys (0.6–1.2 mg/kg p.o.). After pharmacologically active CI-1007 doses, mean plasma CI-1007 C_{max} increased from 19 to 200 ng/ml in Sprague-Dawley rats at doses of 3–30 mg/kg, and from 8.1 to 34 ng/ml in squirrel monkeys at doses of 0.6–1.2 mg/kg, but corresponding plasma M1 C_{max} values were near or below the limit of quantitation (5 ng/ml). CI-1007 EC50 was 31.1 ng/ml in rats, calculated from a log-linear regression. In monkeys, CI-1007 EC_e50, γ, and K_{eo} at 0.6 and 1.2 mg/kg were 4.8 and 4.5 ng/ml, 1.9 and 2.0, and 0.47 and 0.48 hr^{-1}, respectively, calculated by the link model.

Conclusions. CI-1007 has shown dose-related pharmacokinetics and pharmacodynamics in rats and monkeys. Although M1 produces antipsychotic-like effects similar to CI-1007, the contribution of M1 to the activity of the parent drug may not be significant in rats and monkeys as based on plasma levels. CI-1007 plasma concentration correlates log-linearly with inhibition effect from the rat locomotor study. The counter-clockwise hysteresis relationship of CI-1007 plasma concentration and inhibition effect from the monkey avoidance test was described by a link model, and the resulting C_e (concentration in effect compartment) versus effect profile exhibits a sigmoidal curve.

KEY WORDS: antipsychotic; pharmacokinetics; pharmacodynamics; active metabolite; rat; monkey.

INTRODUCTION

CI-1007 is a brain dopamine (DA) autoreceptor agonist and partial dopamine D_2 agonist (1) that is currently under clinical investigation. CI-1007 potently inhibits the firing of DA neurons in rats, locomotor activity in mice and rats, and continuous avoidance in monkeys (2). In contrast to most available antipsychotics, CI-1007 causes only mild extrapyramidal side-effects (EPS) in monkeys (2). CI-1007 is a lipophilic compound with moderate bioavailability and high hepatic clearance (3,4). It penetrates the blood-brain barrier rapidly reaching brain concentrations several times higher than those in plasma, which is consistent with its potent effects on the central DA system. CI-1007 is extensively metabolized to a variety of metabolites after p.o. administration (4,5). PD 147693 (M1), a monohydroxy metabolite, is pharmacologically active (5). In a previous study, pharmacokinetic profiles of CI-1007 and M1 were compared after single i.v. or p.o. administration to rats (4). M1 has a shorter elimination $t_{1/2}$, higher hepatic clearance, and lower bioavailability compared to CI-1007. As a monohydroxy metabolite, M1 may be further metabolized to form a dihydroxy derivative or to form a conjugate.

The objective of this work was to study the pharmacokinetics and pharmacodynamics of CI-1007 following p.o. administration to rats and monkeys. Pharmacological activities and plasma levels of CI-1007 and M1 were also compared. Inhibition of dopamine (DA) neuron firing and spontaneous locomotor activity in rats and inhibition of continuous (Sidman) avoidance in monkeys were selected as animal pharmacodynamic models (2). All three models are commonly used for antipsychotic screening, and the continuous avoidance test in monkeys is considered a key predictor of antipsychotic efficacy. For several known antipsychotics (e.g., haloperidol, chlorpromazine, fluphenazine, risperidone, thioridazine, etc.), a correlation between the ED_{50} doses from the avoidance test in monkeys and the therapeutic dose ranges in humans was observed (6).

MATERIALS AND METHODS

The studies reported in this manuscript adhered to the "Principles of Laboratory Animal Care" (NIH publication #85-23, revised 1985).

Chemicals and Reagents

CI-1007 (PD 143188), pyridine, 1,2,3,6-tetrahydro-4-phenyl-1-[(3-phenyl-3-cyclohexen-1-yl)methyl]-, (R)-(+) enantiomer, and M1 (structures in Fig. 1) were synthesized at Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company (Ann Arbor, Michigan, USA). All solvents and chemicals for HPLC assays were HPLC or analytical grade. Different groups of animals were used for concentration measurement and for pharmacology studies, since blood drawing from test

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ABBREVIATIONS: M1, PD 147693; C_{max}, maximum plasma concentration; t_{max}, time to reach Cmax; $t_{1/2}$, elimination half-life; $AUC_{0\text{-tldc}}$, area under the plasma concentration-time curve from zero to the last detectable concentration; $AUC_{0\text{-}\infty}$, area under the plasma concentration-time curve from zero to infinite time; EPS, extrapyramidal side effects; ED50, the dose which produces 50% of the effect; ED100, the dose which produces 100% of the effect; DA, dopamine; E_{max}, maximum inhibition; EC_e50 is the concentration at half of the maximum effect, K_{eo} is a first-order rate constant used in link model; C_e is concentration in the effect compartment; EC_e50 is the concentration in the effect compartment at half of the maximum effect, and γ is a constant expressing the sigmoidicity of the concentration-effect relationship.

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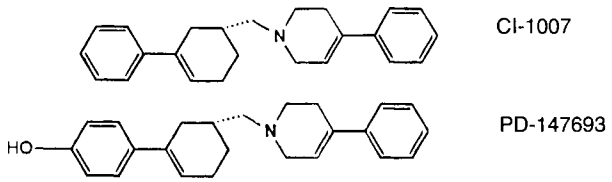

Fig. 1. Structures of CI-1007 and PD 147693 (M1).

animals might complicate the interpretation of pharmacology results.

Electrophysiology

Male Sprague-Dawley rats (200–350 g) were anesthetized with chloral hydrate (400 mg/kg, i.p.) and supplemented as needed. Animals were mounted in a stereotaxic apparatus and a burr hole was drilled in the skull over the substantia nigra. Body temperature was monitored and maintained at 36.5°C to 37.5°C. Extracellular neuronal signals were recorded using a single-barrel glass micropipette. Recordings were made from neurons whose electrophysiological characteristics matched those established from midbrain DA neurons. These action potentials were amplified and counted. Once isolated, the activity of each neuron was monitored for 5 minutes prior to drug injection. The average firing rate during the 2 minutes prior to drug injection was defined as the baseline firing rate. Rats received 2.5 mg/kg CI-1007 (n = 4) or M1 (n = 2) as a single bolus i.p. injection via an indwelling peritoneal catheter, and the neuronal response was monitored until a stable or maximal (100% inhibition) response was obtained. At the end of each experiment, the recording site was marked, and the brain was removed and examined histologically to verify placement. All recording sites were located within the substantia nigra zona compacta.

Pharmacokinetic/Pharmacodynamic Studies in Rats

CI-1007 and M1 were evaluated in a locomotor activity test which has been routinely used to assess the functional activity of antipsychotic agents (2). Fasted male Sprague-Dawley rats (200–300 g, 5 to 12/group) were tested after either vehicle or single p.o. doses of 0.3, 1, 3, 10, or 30 mg/kg CI-1007 or M1, and fasted male Wistar rats (200–300 g, 5 to 12/group) were tested after either vehicle or a single p.o. dose of 10 mg/kg CI-1007. The effects on spontaneous locomotor activity were assessed 1 hr post dosing and the data were recorded for 30 min. Individual rats were placed in darkened cylindrical chambers containing a circular alleyway traversed by six equally spaced photobeams. Six photobeam interruptions generated one activity count. Data are expressed as percent inhibition of spontaneous locomotor activity, relative to controls treated concurrently.

Separate groups of male Sprague-Dawley and Wistar rats (250–300 g) were used for pharmacokinetic studies. Animals were fasted overnight before drug administration. Groups 1 (n = 4), 2 (n = 3), and 3 (n = 4) of Sprague-Dawley rats received single 3, 10, or 30 mg/kg p.o. doses of CI-1007, respectively, and a group (n = 4) of Wistar rats received a single 10 mg/kg p.o. dose of CI-1007. Serial heparinized blood samples were collected predose and at different times up to 28 hours following each dose. After centrifugation, plasma samples were collected and stored at −20°C until analysis for CI-1007 and M1.

Pharmacokinetic/Pharmacodynamic Studies in Squirrel Monkeys

CI-1007 and M1 were evaluated in a monkey continuous avoidance test. Male squirrel monkeys (0.8–1.0 kg) were trained in a modified Sidman avoidance procedure (2) in which the depression of a lever in an operant chamber postponed the delivery of an unsignaled shock (2.0 mA) through a grid floor. During a response-shock component, a shock was delivered when 20 sec elapsed without a response and this switched the schedule to a shock-shock component during which shocks were delivered every 10 sec until a lever press terminated shock delivery and reinstated the response-shock component. Six chronically maintained animals were tested with each drug dose under fasted conditions and were tested no more than once per week. On separate occasions, monkeys (n = 6) received 0.3, 0.6, and 1.2 mg/kg p.o. doses of CI-1007 or 0.94, 1.25, and 1.88 mg/kg of M1 and tested for 6 hr following each dose. Avoidance responding was expressed as the percentage of possible shocks (180 per hr) avoided. Drug effects in each animal were expressed relative to control performance during a previous nondrug session. Mean values of the group were then derived to generate dose-response relationship.

A separate group (n = 4) of male squirrel monkeys (0.8–1.2 kg) was used for the pharmacokinetic study. Fasted monkeys received 0.6, 1.2, and 5.0 mg/kg p.o. doses of CI-1007 in a crossover design with at least a one week washout period between doses. Serial heparinized blood samples were collected predose and at different times postdose via a venous access port implanted in either the external jugular or femoral vein. After centrifugation, plasma samples were collected and stored at −20°C until analysis for CI-1007 and M1.

Assay for CI-1007 and M1 in Plasma

Concentrations of CI-1007 and M1 in rat and monkey plasma were determined using validated liquid chromatographic assays. Minimum quantitation limits of CI-1007 and M1 were 3 and 5 ng/ml, respectively, for a plasma sample volume of 0.100 ml (4,7).

Non-Compartmental Pharmacokinetic Analysis

Maximum plasma CI-1007 concentrations (C_{max}) and times for these to occur (t_{max}) were recorded as observed following each treatment. Elimination-rate constants (λz) were calculated by linear regression of the log-linear terminal phase of the plasma concentration-time profile. Elimination half-life values ($t_{1/2}$) were calculated as 0.693/λz. Area under plasma concentration-time curve from zero to the last detectable concentration ($AUC_{0\text{-tldc}}$) was estimated using the trapezoidal rule. Area under plasma concentration-time curve from zero to infinite time, ($AUC_{0\text{-}\infty}$), was determined by summing $AUC_{0\text{-tldc}}$ and ldc/λz values.

Pharmacokinetic/Pharmacodynamic (PK/PD) Analysis

Sprague-Dawley Rats

ED50 and EC50 were calculated by correlating CI-1007 or M1 dose (D) to the effect (E) or CI-1007 plasma concentration (C) to the inhibition effect (E),

$$E = A \cdot \log(D) + B \quad (1)$$

$$E = A \cdot \log(C) + B \quad (2)$$

Squirrel Monkeys

Plot of CI-1007 plasma concentration versus inhibition effect from monkey avoidance test exhibits a counter-clockwise hysteresis loop (Fig. 8). This suggested an equilibration delay between the central (plasma) and effect compartments. The link model proposed by Sheiner et al (8) was used for PK/PD analysis. The plasma concentration-time profile (0–6 hr) was described by an open one-compartment model with first order absorption,

$$C = A \cdot e^{-ka \cdot t} + B \cdot e^{-k \cdot t} \quad (3)$$

where K_a and K are first-order absorption and elimination rate constants, respectively.

A hypothetical effect compartment was postulated to link indirectly the effect to the central compartment, and the concentration in the effect compartment (C_e) was related to the plasma concentration of the drug (C) via first-order kinetics described by the following equation (8,9):

$$dC_e/dt = K_{eo}(C - C_e) \quad (4)$$

where K_{eo} is a first-order rate constant.

A sigmoid E_{max} model was used for pharmacodynamic modeling.

$$E = (E_{max} \cdot C_e^{\gamma})/(EC_e50^{\gamma} + C_e^{\gamma}) \quad (5)$$

where E is the measured percent inhibition in the monkey continuous avoidance test, and E_{max} is the maximum effect (fixed to 100%). EC_e50 is the concentration in the effect compartment at half of the maximum effect, and γ is a constant expressing the sigmoidicity of the concentration-effect relationship. The plasma concentration data were first fitted to an open one-compartment model using WinNONLIN 1.1 (Scientific Consulting Inc.) and the resulting pharmacokinetic parameters were used in the fitting of C_e and E to the pharmacodynamic model (eqs. 4 and 5).

RESULTS

Effects on DA Neuronal Activity in Sprague-Dawley Rats

Similar to other DA autoreceptor agonists, CI-1007 and M1 inhibited the neuronal firing of substantia nigra zona compacta DA neurons, an effect that could be reversed by haloperidol (2). Both the drug and the metabolite produced nearly complete suppression of the firing activity after an i.p. dose of 2.5 mg/kg to Sprague-Dawley rats (Fig. 2). Approximately 50% inhibition was detected at 6 and 4 min. for CI-1007 and M1, respectively, suggesting that both entered the brain and initiated a central effect rapidly. Slopes from linear regression of the effect versus time plots (Fig. 2) between 20–80% of the effect were 13.6 and 19.5 for CI-1007 and M1, respectively, which suggests that the rate of onset is increased for M1 compared to CI-1007 after comparable doses.

Pharmacokinetics/Pharmacodynamics (PK/PD) in Rats

Sprague-Dawley Rats

Mean (±SD) plasma CI-1007 C_{max} increased proportionally from 19.0 (±7.8) to 200 (±25) ng/ml and $AUC_{0\text{-tldc}}$ increased more than proportionally from 34.8 (±9.8) to 997 (±149) ng·hr/ml in Sprague-Dawley rats, as CI-1007 dose increased from 3 to 30 mg/kg (Table I). In general, CI-1007 was rapidly absorbed (Fig. 3a), and mean (±SD) t_{max} values were 0.44 (±0.37), 1.3 (±0.6), and 2.5 (±0.6) hr at 3, 10, and 30 mg/kg, respectively. The prolonged t_{max} at higher doses is suggestive of a prolonged absorption phase. Mean (±SD) CI-1007 elimination $t_{1/2}$ was 10.7 (±4.5) hr at 30 mg/kg, which is similar to the $t_{1/2}$ (9.3 hr) obtained from an i.v. experiment (3). The long terminal phase was not identified at lower doses. Plasma M1 concentrations were below the limit of quantitation (<5 ng/ml) at 3 or 10 mg/kg, and low at 30 mg/kg in CI-1007 treated Sprague-Dawley rats. Mean (±SD) M1 plasma C_{max} and $AUC_{(0\text{-tldc})}$ at 30 mg/kg were 11.1 (±1.6) ng/ml and 44.7 (±13.1) ng·hr/ml, respectively, which are approximately

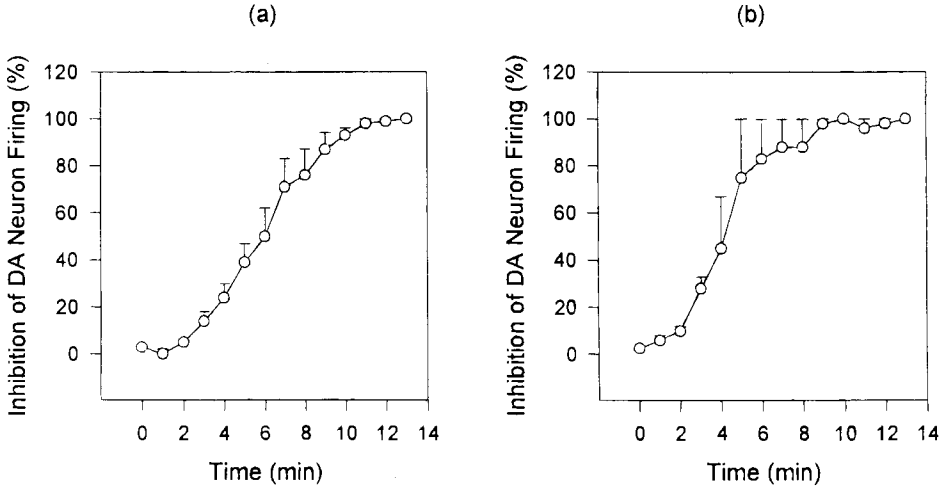

Fig. 2. Effects of CI-1007 (a) and PD 147693 (M1) (b) on DA neuronal activity following a single i.p. dose of 2.5 mg/kg to Sprague-Dawley rats. Each point is the mean ± S.E.M. (n = 4 and 2 for Fig. 2a and 2b, respectively).

Table I. Mean (±SD) (n = 3–8) CI-1007 Pharmacokinetic Parameters Following Single 3, 10, or 30 mg/kg p.o. Doses of CI-1007 to Sprague-Dawley or Wistar Rats

Parameter	Sprague-Dawley rats			Wistar rats
	3 mg/kg	10 mg/kg	30 mg/kg	10 mg/kg
C_{max} (ng/ml)	19.0 (±7.8)	52.9 (±13.2)	200 (±25)	80.2 (±28.7)
C_{max}/dose	6.3	5.3	6.7	8.0
t_{max} (hr)	0.44 (±0.37)	1.3 (±0.6)	2.5 (±0.6)	1.3 (±0.6)
$t_{1/2}$ (hr)	—[a]	4.3 (±2.5)	10.7 (±4.5)	4.9 (±1.9)
$AUC_{0\text{-tldc}}$ (ng·hr/ml)	34.8 (±9.8)	192 (±62)	997 (±149)	288 (±60)
$AUC_{0\text{-tldc}}$/dose	11.6	19.2	33.2	28.8
$AUC_{0\text{-}\infty}$ (ng·hr/ml)	—[a]	216 (±74)	1080 (±150)	322 (±73)

[a] $t_{1/2}$ and AUC were not calculated due to insufficient number of data points.

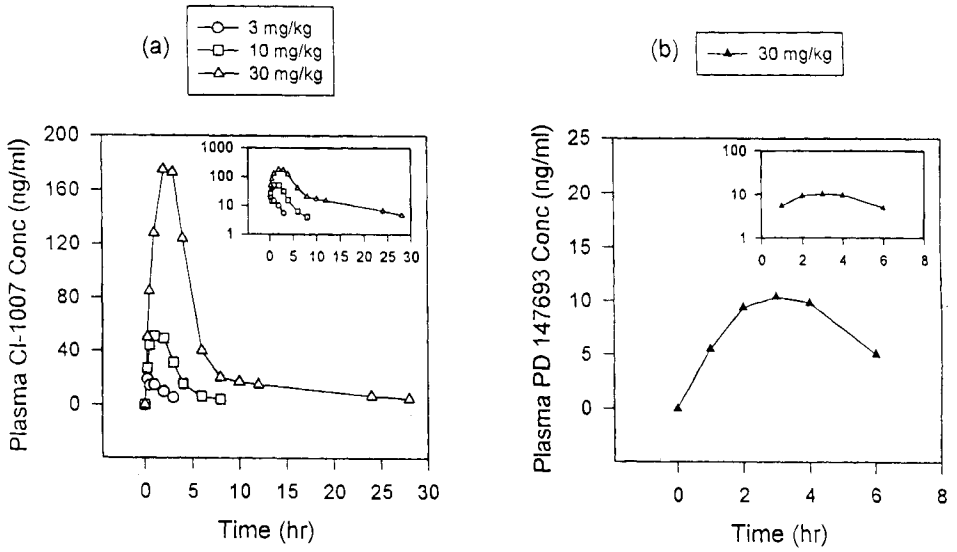

Fig. 3. Mean (n = 3 − 4) plasma CI-1007 (a) and PD 147693 (M1) (b) concentration versus time profiles in Sprague-Dawley rats following single p.o. doses of 3, 10, or 30 mg/kg CI-1007, plotted on rectilinear and semi-logarithmic (inserted) scales. Mean PD 147693 concentrations were below the limit of quantitation at 3 and 10 mg/kg.

twenty-fold lower than those of the parent drug. Mean (±SD) plasma M1 t_{max} was 3.0 (±0.8) hr at 30 mg/kg, which is similar to that of CI-1007. M1 elimination $t_{1/2}$ was not calculated due to limited data points.

CI-1007 and M1 have shown dose-related effects on spontaneous locomotor activity following p.o. administration (Fig. 4a, 4b). ED50 doses (eq. 1) were 6.2 and 9.1 mg/kg for CI-1007 and M1, respectively. Since plasma concentrations of M1 were low after p.o. administration of CI-1007, the contribution of M1 to the effects of the parent drug may not be significant. As shown in Fig. 4c, a log-linear correlation of CI-1007 plasma concentration versus the inhibition effect was established. CI-1007 EC50 concentration, calculated from the log-linear regression (eq. 2), was 30.1 ng/ml. No delayed effect was observed in the rat locomotor activity study. Maximum inhibition was detected within 30 min following intravenous (i.v.) or p.o. administration of CI-1007 to rats. The effect declined in a similar fashion compared to CI-1007 plasma concentration profile (10).

Wistar Rats

CI-1007 plasma concentration versus time profile following a single 10 mg/kg p.o. dose to Wistar rats is shown in Fig. 5. Mean (±SD) CI-1007 plasma C_{max}, t_{max}, $t_{1/2}$, and $AUC_{(0\text{-tldc})}$ are comparable to those determined in Sprague-Dawley rats (Table I). Plasma M1 concentrations were also low (<5 ng/ml) in CI-1007 treated Wistar rats. The comparable pharmacokinetic profiles suggest a similar hepatic metabolism of CI-1007 in Sprague-Dawley and Wistar rats, which is consistent with literature data that liver cytochrome P-450 monooxygenase activities are similar for the 2 strains (11).

CI-1007 inhibits 57% of the spontaneous locomotor activity in Wistar rats following a single 10 mg/kg p.o. dose, which is similar to that (53%) observed in Sprague-Dawley rats at the same dose. Both Sprague-Dawley and Wistar rats are often used in antipsychotic drug development. Sometimes one strain will be used in pharmacology screening, while the other one will be used for toxicology studies, therefore it is interesting

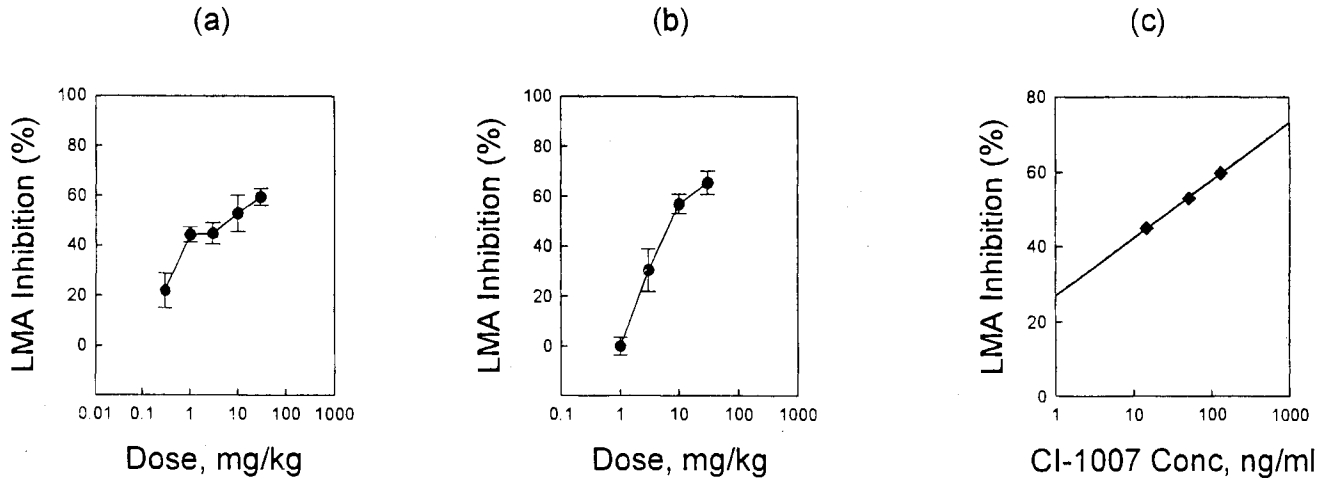

Fig. 4. Dose-response (a, b) and concentration-response (c) plots for inhibition of spontaneous locomotor activity (LMA) following single p.o. doses of CI-1007 (a, c) or PD 147693 (M1) (b) to Sprague-Dawley rats. Each point is the mean ± S.E.M (n = 5 − 17) for effects, which were assessed 1 hr–1.5 hr postdose. The mean effect at 3, 10, and 30 mg/kg were correlated with corresponding mean (n = 4) plasma CI-1007 concentrations at 1 hr post dose (c).

to compare the plasma concentration and locomotor effects in these two strains. Results from our experiments demonstrate comparable pharmacokinetics and pharmacodynamics for the two strains.

Pharmacokinetics/Pharmacodynamics (PK/PD) in Monkeys

Mean plasma CI-1007 and M1 concentration versus time profiles following p.o. doses of 0.6, 1.2 or 5 mg/kg CI-1007 to squirrel monkeys are shown in Fig. 6. CI-1007 was rapidly absorbed with mean t_{max} less than 1.0 hr at all doses. Dose-dependent pharmacokinetics were observed with the other

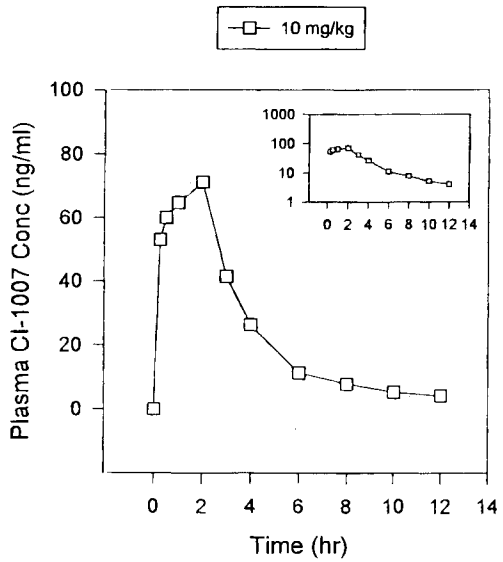

Fig. 5. Mean (n = 4) plasma CI-1007 concentration versus time profile in Wistar rats following single p.o. administration of 10 mg/kg CI-1007, plotted on rectilinear and semi-logarithmic (inserted) scales. Mean PD 147693 (M1) concentration was below the limit of quantitation at 10 mg/kg.

parameters. Mean (±SD) plasma CI-1007 C_{max} and $AUC_{0\text{-tldc}}$ values increased more than proportionally from 8.1 (±2.4) to 112 (±119) ng/ml and from 10.0 (±6.5) to 404 (±236) ng·hr/ml, respectively, as CI-1007 dose increased from 0.6 to 5 mg/kg. Mean (±SD) CI-1007 elimination half-life ($t_{1/2}$) was 23.6 (±10.2) hr at 5 mg/kg, which is similar to the $t_{1/2}$ (22.0 hr) obtained from an i.v. study in squirrel monkeys (3). The long terminal phase was not identified at lower doses.

Following p.o. administration of CI-1007 to squirrel monkeys, mean M1 plasma concentrations were below the limit of quantitation (<5 ng/ml) at 0.6 and 1.2 mg/kg, which suggests that M1 concentrations were less that 15% of those of the parent drug at 1.2 mg/kg and might be even lower at 0.6 mg/kg. Plasma M1 C_{max} and AUC were approximately 20–30% of those of the parent drug at 5 mg/kg. Mean (±SD) plasma M1 C_{max} was 34.0 (±23.1) ng/ml and $AUC_{0\text{-tldc}}$ was 124 (±78) ng·hr/ml at 5 mg/kg. Mean M1 t_{max} (0.87 ± 0.25 hr) was similar to that of CI-1007, and mean M1 $t_{1/2}$ (3.5 ± 0.5 hr) was shorter than that of the parent drug.

CI-1007 and M1 produced dose-related inhibition of continuous avoidance after p.o. administration to squirrel monkeys (Fig. 7). ED50 doses were 0.6 and 1.3 mg/kg for CI-1007 and M1, respectively. Maximum inhibition (E_{max}) was observed between 3 and 4 hr postdose. The contribution of M1 to the inhibition effect of the parent drug on continuous avoidance may not be significant as M1 plasma levels were low at pharmacologically active CI-1007 doses.

A delayed effect was observed when comparing the effect-time and plasma concentration-time profiles in monkeys (Figs. 6, 7). Mean CI-1007 plasma concentrations peaked at 1.0 and 0.88 hr following 0.6 and 1.2 mg/kg oral doses (Table II), while maximum inhibition was detected during the third and fourth hours postdose, respectively. Since M1 has a t_{max} similar to and $t_{1/2}$ shorter than the parent drug, it may not contribute to the delay.

A hypothetical effect compartment was used to link plasma CI-1007 concentration and the effect. The concentrations were first fitted to an open one-compartment model (eq. 3) and the

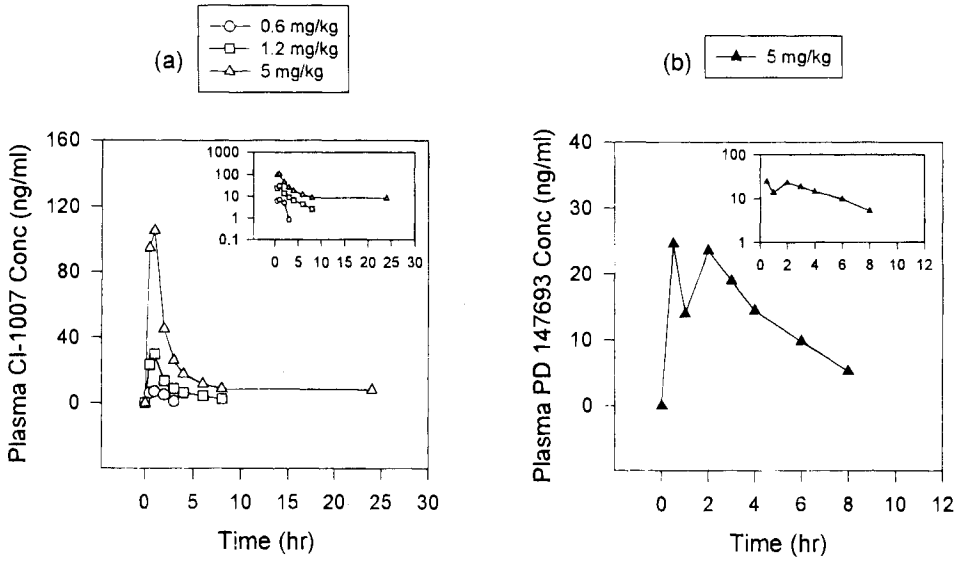

Fig. 6. Mean (n = 4) plasma CI-1007 (a) and PD 147693 (M1) (b) concentration versus time profiles in squirrel monkeys following single p.o. doses of 0.6, 1.2 and 5 mg/kg of CI-1007, plotted on rectilinear and semi-logarithmic (inserted) scales. Mean PD 147693 concentration was below the limit of quantitation at 0.6 and 1.2 mg/kg.

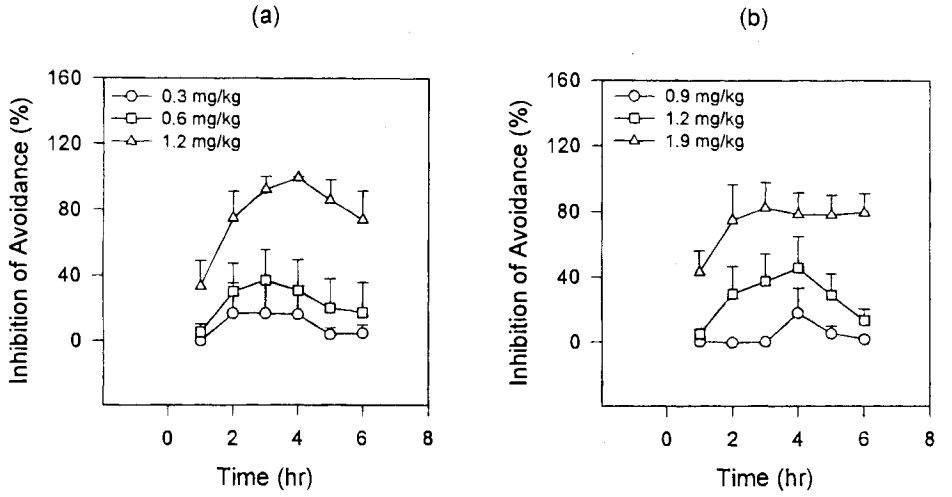

Fig. 7. Response-time curves for inhibition of continuous avoidance following single p.o. doses of CI-1007 (a) or PD 147693 (M1) (b) to squirrel monkeys. Each point is the mean ± S.E.M (n = 6).

Table II. Mean (±SD) (n = 4) CI-1007 Pharmacokinetic Parameters Following Single 0.6, 1.2 and 5 mg/kg p.o. Doses of CI-1007 to Squirrel Monkeys

Parameter	0.6 mg/kg	1.2 mg/kg	5 mg/kg
C_{max} (ng/ml)	8.1 (±2.4)	34.1 (±15.5)	112 (±119)
C_{max}/dose	13.5	28.4	22.4
t_{max} (hr)	1.0 (±0.7)	0.88 (±0.25)	0.75 (±0.29)
$t_{1/2}$ (hr)	—[a]	3.4 (±2.0)	23.6 (±10.2)
$AUC_{0\text{-tldc}}$ (ng·hr/ml)	10.0 (±6.5)	74.3 (±46.4)	404 (±236)
$AUC_{0\text{-tldc}}$/dose	16.7	61.9	80.8
$AUC_{0\text{-}\infty}$ (ng·hr/ml)	—[a]	111 (±75)	703 (±340)

[a] $t_{1/2}$ and AUC were not calculated due to insufficient number of data points.

resulting pharmacokinetic microconstants (k_a = 1.7 and 1.6, k = 0.70 and 0.65 at 0.6 and 1.2 mg/kg, respectively) were used for simultaneous fitting of pharmacokinetic and pharmacodynamic data. Results from PK/PD model fitting (eqs. 4,5) are shown in Figs. 8 and 9 and Table III. The curves of plasma concentration (C), concentration at effect site (C_e), and effect

Table III. CI-1007 Pharmacodynamic Parameters in Squirrel Monkeys Using a Link Model

Parameter	0.6 mg/kg	1.2 mg/kg
EC_e50 (ng/ml)	4.8	4.5
K_{eo} (hr^{-1})	0.47	0.48
γ	1.9	2.0

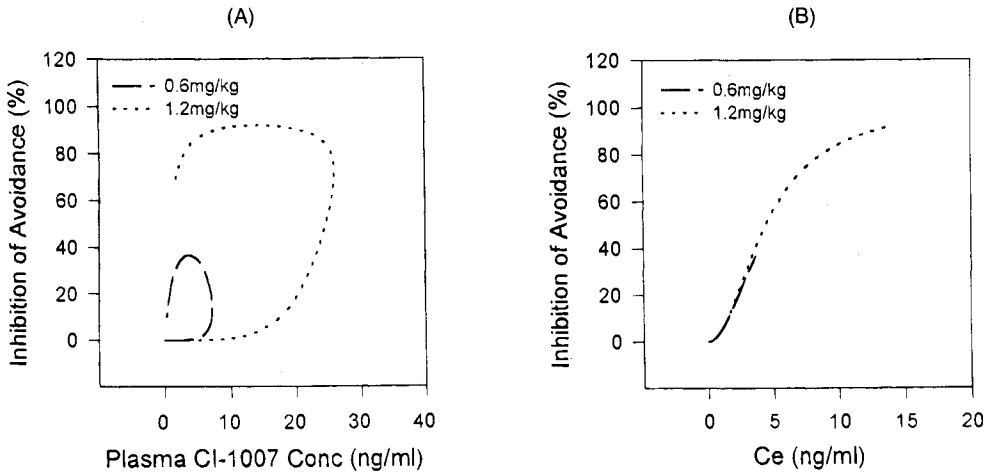

Fig. 8. Hysteresis plots of CI-1007 plasma concentration versus effect from squirrel monkey avoidance test(a), and the sigmoid correlation between the concentration at effect site (C_e) and effect (b). Model (eqs. 3–5) predicted values were used for the plots.

(E) versus time in Fig. 9 represent the predicted C, C_e, and E for the best fit of the data to the proposed link model. Inspection reveals excellent agreement between observed and fitted C and E. CI-1007 EC_e50, γ, and K_{eo} at 0.6 and 1.2 mg/kg were 4.8 and 4.5 ng/ml, 1.9 and 2.0, and 0.47 and 0.48 hr^{-1}, respectively (Table III). Since dose dependent pharmacokinetics were observed, concentration and effect data at each dose were fitted to the equations separately. As shown above, the resulting microconstants and the pharmacodynamic parameters are similar at 0.6 and 1.2 mg/kg.

Although different groups of animals were used for pharmacokinetic and pharmacodynamic studies, rats and monkeys of different groups were assumed to behave similarly in locomotor activity and avoidance tests, since interanimal variability is relatively low for both tests. Similar pharmacokinetic and pharmacodynamic profiles were observed from studies conducted on separate occasions (3,4,10).

DISCUSSION

CI-1007 was rapidly absorbed after p.o. administration showing similar t_{max} in rats and monkeys at lower doses ($\leq$10 mg/kg). Prolonged absorption was observed in rats at the high dose (30 mg/kg) but not in monkeys. CI-1007 has a higher clearance and shorter elimination $t_{1/2}$ in rats (3), which is consistent with plasma CI-1007 C_{max}/dose and AUC/dose in rats being lower than the corresponding values in monkeys (Table I, II). Dose-dependent pharmacokinetics were observed in rats and monkeys, which may be related to saturation of a first-pass at higher doses, since hepatic metabolism is the major route of elimination for this drug (3,4,12).

CI-1007 and M1 have shown nearly complete inhibition on dopamine neuron firing at 2.5 mg/kg i.p., and produced dose-related effects on spontaneous locomotor activity in rats (0.3–30 mg/kg, p.o.) and on continuous avoidance in monkeys

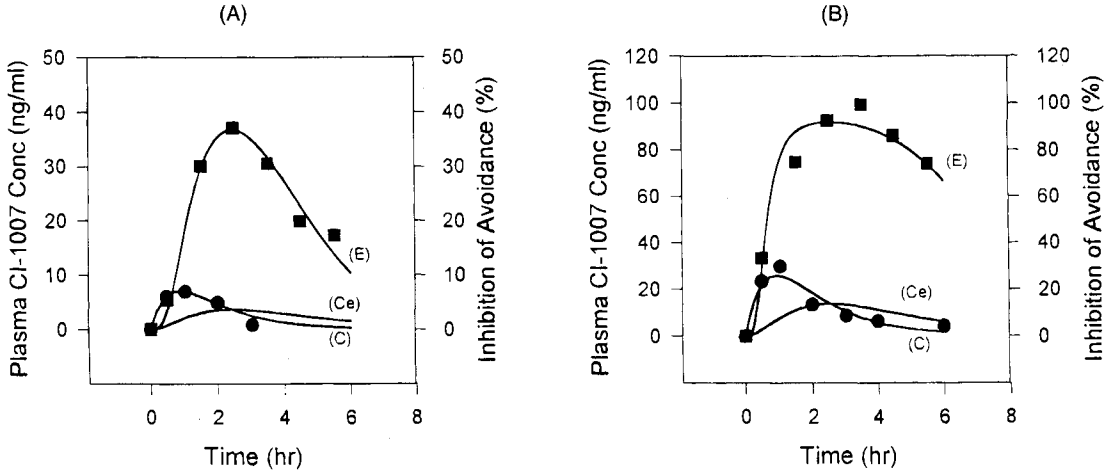

Fig. 9. CI-1007 plasma concentration (C), concentration at effect site (C_e), and effect (E) versus time curves from simultaneous pharmacokinetic and pharmacodynamic model fitting. The data depicted by • are actual mean CI-1007 plasma concentration and by ■ are actual mean effect (inhibition on continuous avoidance) determined in squirrel monkeys at 0.6 (a) and 1.2 (b) mg/kg of CI-1007, respectively. The lines represent the best fit of the proposed model to the data.

(0.6–1.2 mg/kg p.o.). ED50 doses for CI-1007 and M1 were 6.2 and 9.1 mg/kg for the rat locomotor study and 0.6 and 1.3 mg/kg for the monkey avoidance test, respectively. After pharmacologically active CI-1007 doses, mean plasma CI-1007 C_{max} increased from 19 to 200 ng/ml in Sprague-Dawley rats at doses of 3–30 mg/kg, and from 8.1 to 34 ng/ml in squirrel monkeys at doses of 0.6–1.2 mg/kg. Corresponding plasma M1 C_{max} were less than 5% and 15% of those of the parent drug in rats and monkeys, respectively. Therefore, the overall contribution of M1 to the activity of the parent drug may not be significant in rats and monkeys.

CI-1007 plasma concentration correlates log-linearly with the inhibition effect from the rat locomotor test (Fig. 4c), and the calculated EC50 concentration was 30.1 ng/ml in rats. Plots of CI-1007 plasma concentration versus inhibition effect from the monkey avoidance test at 0.6 and 1.2 mg/kg exhibit counterclockwise hysteresis loops (Fig. 8a). This suggested an equilibration delay between the central (plasma) and effect compartments, and the link model was used for PK/PD analysis. The resulting EC_e50 (4.8 and 4.5 ng/ml), K_{eo} (0.47 and 0.48 hr^{-1}), and γ (1.9 and 2.0) values are similar at the two doses. In addition, the two sigmoid curves of the calculated C_e versus effect in Fig. 8b are almost superimposable, suggesting that the link model allows successful PK/PD modeling at both 0.6 and 1.2 mg/kg. The small K_{eo} values suggest that the effect is not directly proportional to the amount of drug in the central compartment (13). Due to limited data points, only a simple link model was used here (9). Results from previous (1,2) and current studies demonstrated that CI-1007 entered the brain and initiated a central effect on DA neuronal activity rapidly, so brain distribution may not be a slow rate limiting factor for equilibration delay. In addition, no delayed effect was observed in the rat locomotor activity test, so the hysteresis loop of CI-1007 concentration versus inhibition effect in monkeys might be caused by a complex mechanism related to the continuous avoidance test. A delayed effect was also observed in the monkey avoidance test after intravenous administration of CI-1007 (2,3).

It is known that during antipsychotic therapy, drug doses needed for therapeutic effects and doses eliciting significant adverse effects vary widely in patients. This may be related to the large differences in plasma levels that patients demonstrate after receiving similar doses of an antipsychotic drug, thus underscoring the importance of monitoring drug and any active metabolite(s) levels during antipsychotic therapy. Although therapeutic plasma concentrations of many antipsychotic drugs can be found in the literature (14–19), drug concentrations in animals at pharmacologically active doses are rarely reported, thus preventing the comparison of drug levels of known antipsychotics in humans and animals. The results of our studies may add some information to this field, which could be very useful for new antipsychotic drug development.

ACKNOWLEDGMENTS

We thank Dr. Stephen Olson for his valuable comments on the paper.

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