

The Pharmacokinetics and Bioavailability of Prochlorperazine Delivered as a Thermally Generated Aerosol in a Single Breath to Volunteers

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A thermally generated aerosol (TGA) system can effect reliable delivery of excipient-free drug to alveoli, resulting in rapid systemic drug absorption. We developed a pharmacokinetic model of prochlorperazine, administered by inhalation and as a rapid intravenous infusion, and we determined absolute TGA bioavailability in eight healthy volunteers in this institutional review board–approved, two-period crossover study. After the drug was administered as either a 5-s intravenous infusion or a TGA single-breath inhalation, blood was collected at various times for up to 24 h. Plasma prochlorperazine concentrations were measured using liquid chromatography–tandem mass spectrometry. Inhalation and rapid intravenous administration produced similar plasma prochlorperazine concentration profiles. Intravenous and inhalation pharmacokinetics were well characterized by a simultaneous two-compartment model with multiple absorption delays. Prochlorperazine pharmacokinetic parameters were similar to those reported for single intravenous doses. The geometric mean bioavailability after TGA delivery was 1.10. The administration of prochlorperazine by inhalation resulted in pharmacokinetics similar to that seen after intravenous administration, in terms of speed, extent, and consistency of absorption.

Prochlorperazine has been reported to relieve acute migraine attacks when administered intravenously in an emergency department setting.^{1–3} Orally administered prochlorperazine is of limited use for such acute therapy because of its slow absorption and low bioavailability consequent to high hepatic extraction.^{4,5} A different mode of prochlorperazine administration that can produce effective plasma drug concentrations as rapidly and predictably as those provided by intravenous administration might offer a valuable therapeutic alternative to intravenous administration for the treatment of an acute migraine attack, especially if it could be used safely by the patient without the assistance or supervision of a medical professional.

Rapid systemic drug delivery has until now been accomplished largely through intravenous administration. However, recent advances in devices that facilitate systemic drug delivery by inhalation may provide an alternative to intravenous administration when it is necessary to have fast, predictable production

of effective plasma drug concentrations.⁶ An important feature of such devices is their ability to produce aerosol particles of a size (1–3 μm in diameter) that allows efficient deposition in the alveoli, from where they are absorbed rapidly into the systemic circulation.⁷ Devices that have been developed to do this include jet and ultrasonic nebulizers, metered-dose inhalers, and dry-powder inhalers, all of which have been relatively inefficient in delivering drug to the alveoli and have other practical disadvantages.⁸ A significant advance in alveolar drug delivery technology has been the development of a device capable of rapid, reliable systemic delivery of pure drug through production of a thermally generated aerosol (TGA) for inhalation.^{9,10} This device rapidly vaporizes a thin film of drug at a relatively low temperature to produce a pure drug vapor that cools and condenses into 1–3 μm mass median aerodynamic diameter aerosol particles that can be inhaled in a single breath and absorbed systemically. This process is capable of producing peak plasma drug concentrations at least as rapidly as those produced by a

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5-s intravenous administration and can also deliver the drug at >80% bioavailability.^{10,11}

We have developed a pharmacokinetic model that describes pulmonary prochlorperazine absorption after TGA inhalation delivery in dogs. The model uses a tanks-in-series delay element to characterize the noninstantaneous first appearance of the drug in the body.¹¹ The purpose of this study was to describe the pharmacokinetics of prochlorperazine administered by inhalation to healthy volunteers and to determine the absolute bioavailability of the drug when it is administered in this manner.

RESULTS

Plasma prochlorperazine concentrations after administration by single-breath inhalation increased at least as rapidly as those after a 5-s intravenous infusion (Table 1). Following intravenous administration, plasma drug concentrations were observed to peak at an average level of 1.06 ng/ml after an average time interval of 3.50 min. Following administration by inhalation, the peak plasma drug concentration averaged 1.38 ng/ml after an average time interval of 2.00 min. After peaking, the concentrations declined and oscillated in parallel, with venous plasma drug concentrations from the 5-s intravenous administration being slightly lower than those from administration by inhalation over the entire observation period.

Upon inspection of the plasma prochlorperazine concentration vs. time data following administration by single-breath inhalation and by 5-s intravenous administration, it was clear that the single absorption delay element model that had been developed to describe prochlorperazine disposition after administering the drug via both of these routes in dogs¹¹ could not describe the multiple peaks observed after prochlorperazine administration via similar routes in human volunteers. It was therefore decided to first develop a model that would fit the data generated after drug administration by inhalation in humans.

When the single absorption delay element model (Figure 1) was fitted to plasma prochlorperazine concentration vs. time data obtained after administration by inhalation, it resulted in systematic overprediction of drug concentrations in the first

hours after drug administration, followed by a period of systematic underprediction, and again subsequently by a period of overprediction (Figure 2). The addition of a second absorption delay element (Figure 1) improved the fit of the model, but there was still a significant systematic error, generally in the first 2 h after drug administration (Figure 2). A third absorption delay element was therefore added to the model (Figure 1), improving its fit by eliminating the systematic error in the earlier fits (Figure 2). The Akaike information criterion and the Schwarz–Bayesian information criterion supported the appropriateness of the choice of the model with three absorption delay elements. The final model (Figure 1), therefore, included fast-, intermediate-, and slow-absorption delay elements.

The final model developed for inhalational dosing (Figure 1) was subsequently used to describe the disposition

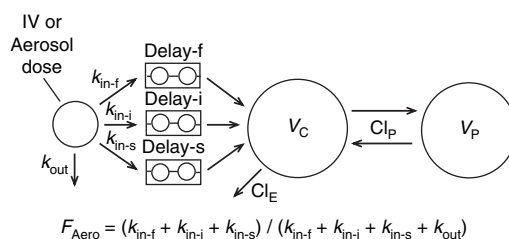


Figure 1 The two-compartment pharmacokinetic model used for the simultaneous analysis of the pharmacokinetics of prochlorperazine administered as a thermally generated aerosol single-breath inhalation and as a 5-s intravenous infusion to the same subject at different times. Drug delivery was modeled as the proportion of drug absorbed through fast- (f), intermediate- (i), and slow-delay (s) elements (represented by rectangles surrounding two cells) to describe the noninstantaneous appearance of the drug in the body due to multiportion absorption of the various doses. In the model, k_{in-f} , k_{in-i} , and k_{in-s} were adjusted, along with the other parameters describing the pharmacokinetic data for each dose for each subject. The sums ($k_{in} = k_{in-f} + k_{in-i} + k_{in-s}$) were constrained to equal 1 for the intravenous administration and unconstrained for the aerosol (F_{Aero}). F_{Aero} therefore defines the bioavailability of prochlorperazine when administered as an aerosol.

Table 1 Initial peak plasma drug concentration characteristics of 0.5 mg of prochlorperazine (nominal dose, 0.625 loaded aerosol dose) delivered as a 5-s intravenous infusion and as a thermally generated aerosol in a single breath

Route of drug administration	Observed		Predicted by pharmacokinetic model	
	Initial t_{max} (min)	Initial C_{max} (ng/ml)	Initial t_{max} (min)	Initial C_{max} (ng/ml)
Intravenous over 5 seconds	3.50 ± 2.88	1.06 ± 0.84	3.16 ± 2.10	1.03 ± 0.78
Aerosol in a single breath	2.00 ± 0.76	1.38 ± 0.56	1.74 ± 1.15	1.56 ± 0.54
Difference (IV–aerosol) ^a	0.127	0.303	0.028	0.075
P value				

Data are listed as mean ± SD ($n = 8$).

^aDifference between IV and aerosol by paired t -test.

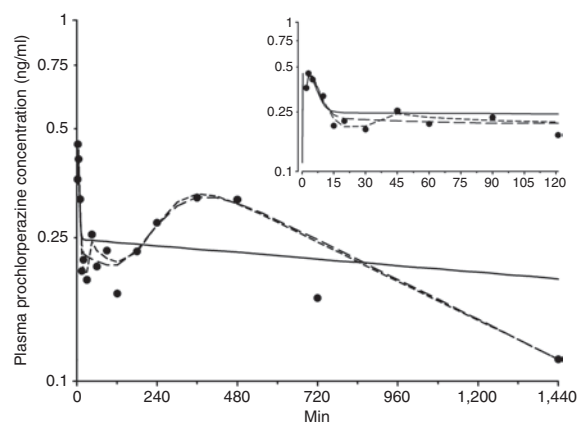


Figure 2 Plasma prochlorperazine concentration history for the first 24 h after administration as a thermally generated aerosol single-breath inhalation to a volunteer. The symbols represent observed values, the solid lines represent values predicted by the single delay model, the long broken lines represent values predicted by the dual delay model, and the short broken lines represent values predicted by the triple delay model.

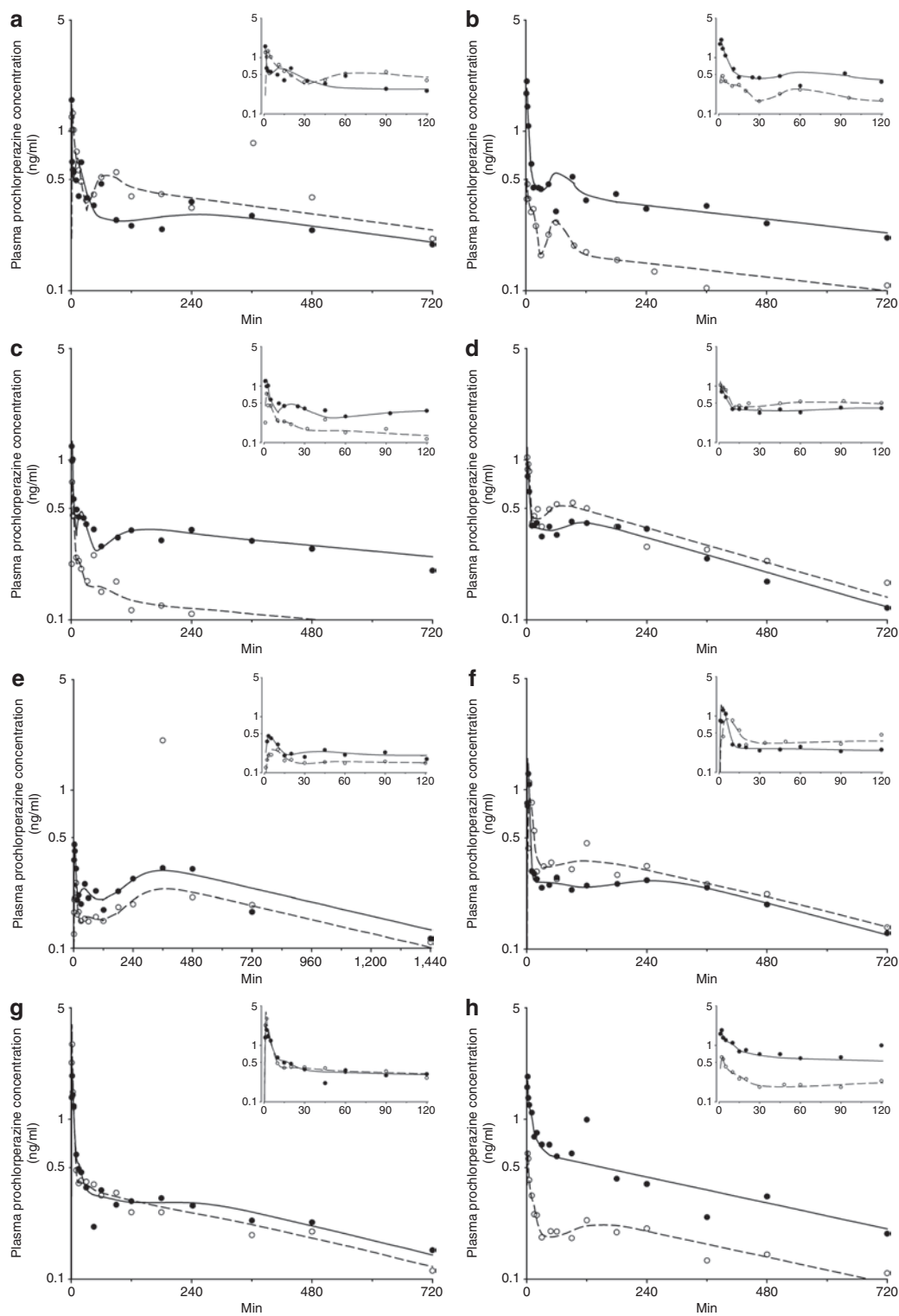


Figure 3 Plasma prochlorperazine concentration history for 12–24 h after drug administration as a thermally generated aerosol delivered as a single-breath inhalation (0.625 mg) and as a 5-s intravenous infusion (0.5 mg) in two separate sessions to each of the eight subjects (a–h). The closed circles represent observed values, the solid lines represent predicted values for the thermally generated aerosol dose, the open circles represent observed values, and the long broken lines represent predicted values for the 5-s intravenous dose.

of prochlorperazine after both inhalation and a 5-s intravenous administration, simultaneously for each subject (Figure 3). Although both routes of prochlorperazine administration were constrained to have the same two-compartment

pharmacokinetic model in each subject, independent mean transit times (MTTs) and splits were allowed for the three absorption delay elements for each route of administration. Table 2 shows the pharmacokinetic parameters for the simultaneous model of

Table 2 Prochlorperazine pharmacokinetic parameters for the combined model

Volumes (l) ^a			Clearances (l/min) ^b			
V_C	V_P	V_{SS}	Cl_P	Cl_E	$t_{1/2\beta}$ ^c (h)	F_{aero} ^d
74.9 ± 60.8	1,547 ± 852	1,621 ± 890	55.5 ± 21.3	1.91 ± 0.56	10.3 ± 4.5	1.10 (0.72–1.69)

Data are presented as mean ± SD ($N = 8$).

^aThe volumes (V) of the central (C) and peripheral (P) compartments and the volume of distribution at steady state (V_{SS}), which is the sum of all volumes. ^bThe clearance of the peripheral compartment (Cl_P) and elimination clearance (Cl_E). ^cElimination half-life. ^dBioavailability of prochlorperazine administered by inhalation, expressed as geometric mean (95% confidence interval).

Table 3 Absorption delay element mean transit times (MTTs) and splits (% dose) for the two means of prochlorperazine administration

Dose and means of administration	Delay element MTT (min)			Delay element split (% dose)		
	Fast absorption	Intermediate absorption	Slow absorption	Fast absorption	Intermediate absorption	Slow absorption
0.5 mg intravenous over 5 s	3.31 ± 3.48	31.2 ± 36.6	170 ± 140	39.6 ± 23.5	29.7 ± 12.3	30.6 ± 18.0
0.625 mg aerosol in a single breath	1.76 ± 2.19	23.0 ± 19.0	160 ± 95	35.4 ± 17.2	31.3 ± 17.2	33.4 ± 11.5

Data are presented as mean ± SD ($n = 8$).

prochlorperazine disposition after administration by inhalation and after 5-s intravenous administration. The maximum plasma drug concentrations (C_{max}) predicted by the model were 1.03 ng/ml and 1.56 ng/ml for the intravenous infusion and inhalation routes, respectively, and the corresponding predicted times to maximum concentration (t_{max}) averaged 3.16 min and 1.74 min, respectively (Table 1). The MTTs of the absorption delay elements and the split of the absorption among them were similar for the two routes of administration (Table 3). That is, for the intravenous and the inhalational routes, the average MTTs for the fast-absorption delay element were 3.31 and 1.76 min, respectively; the average MTTs for the intermediate-absorption delay element were 31.2 and 23.0 min, respectively; and the average MTTs for the slow-absorption delay element were 170 and 160 min, respectively. For the intravenous and the inhalational routes, the average fast-absorption splits (percentage of dose) were 39.6 and 35.4%, respectively; the average intermediate-absorption splits were 29.7 and 31.3%, respectively; and the average slow-absorption splits were 30.6 and 33.4%, respectively.

Bioavailability estimates were based on the loaded prochlorperazine dose of 0.625 mg (Table 2). The geometric mean bioavailability was 1.10, with a 95% confidence interval of 0.72–1.69.

DISCUSSION

The administration of prochlorperazine to volunteers by single-breath inhalation produced venous plasma drug concentrations similar to those produced by a 5-s intravenous administration of the same nominal dose as the emitted dose of the drug, at least as rapidly and as predictably (Table 1, Figure 3). The good simultaneous fit of the same two-compartment pharmacokinetic model to the venous plasma prochlorperazine concentration vs. time data after both aerosol and intravenous administration—without systematic deviations of the observed data from the calculated values and without model misspecification (Figure 3)—suggests that the distribution pharmacokinetics of the drug is unaffected

by the route of administration. In this study, the volume of distribution and elimination clearance of prochlorperazine are very similar to those reported by others.^{4,5,12}

The geometric mean bioavailability of prochlorperazine administered by inhalation to volunteers was 1.10 of the coated dose, despite *in vitro* evidence that the emitted dose was only 80% of the coated dose. At least one other study of pulmonary drug delivery found complete bioavailability of the nominal dose despite an *in vitro* estimate that bioavailability would be 50% of that dose, but it had no testable explanation for this observation.¹³

An interesting aspect of this study is the fact that the model that had been used for simultaneously fitting data obtained from intravenous and aerosol prochlorperazine administration in dogs¹¹ did not fit similarly obtained data from humans. An obvious difference in the disposition of prochlorperazine noted in the two studies was in its volume of distribution at steady state, which averaged ~1.71/kg in dogs¹¹ and 20.71/kg in the human volunteers. The multiple prochlorperazine peaks that were noted and the need for a more complex description of systemic absorption to characterize them may be related to the considerably larger volume of distribution of the drug in humans.

Oscillations in drug concentration vs. time data following a single brief dose, such as those observed in this study, represent disruptions of the disposition processes that are represented by models requiring the assumptions of complete and instantaneous mixing within compartments and constant clearances between and out of compartments. An example on a very short time scale is the one representing linked processes of pulmonary uptake and intravascular mixing that result in oscillating blood drug concentrations. These cannot be characterized by a model that assumes complete and instantaneous mixing.¹⁴ Incorporating delay elements into a pharmacokinetic model permits a scenario in which the drug spends time outside of the continuous system and, when it enters, a surge in blood drug concentration (an oscillation) may be observed.

The relatively early and frequent sampling carried out in this study was critical to the present modeling of multiportion prochlorperazine absorption (discussed below). Three parallel absorption processes, each of which had a variable number of nondiscrete (i.e., tanks-in-series) delay elements, in the pharmacokinetic models enabled the description of the multiple drug concentration peaks observed after administration, whether intravenously or by inhalation. These delays provide drug molecule transit time frequency histograms that portray the fraction of drug molecules arriving at the sampling point over time. There is only one fastest transit time (discrete lag), but some transits can be quite delayed, resulting in a distribution that is skewed to the right and that can be described statistically by a gamma distribution function. For a right-skewed distribution, the mean value (mean transit time) is longer than (to the right of) the peak concentration (C_{\max} or the mode of the frequency distribution). As a result, the times to peak or maximum concentrations (e.g., t_{\max} in [Table 1](#)), can be shorter than the corresponding MTTs ([Table 3](#)).

Mather *et al.* described the systemic disposition of fentanyl, a lipophilic basic amine like prochlorperazine, after administration to volunteers both intravenously and in an aerosol delivered from a metered-dose inhaler and made several observations similar to those in this study.¹⁵ For example, they found secondary plasma fentanyl concentration peaks after both intravenous and aerosol fentanyl administration in some patients. They calculated fentanyl bioavailability as a function of time after aerosolized fentanyl input, with 56% bioavailability at 5 min, 66% at 20 min, 83% at 60 min, and 96% at 360 min. As a result, they concluded that pulmonary fentanyl absorption might be better described by a multiphasic input, with a portion of the drug being absorbed rapidly, another portion being absorbed more slowly, and the rest being absorbed even more slowly. Although they were unable to model the multiphasic input from their data, the intensive sampling in this study supports that approach ([Figure 1](#)).

Although multiple peaks have been observed after oral¹⁶ and epidural¹⁷ drug administration, it is generally expected that plasma drug concentrations will continually decrease with time after termination of intravenous drug administration and completion of intravascular mixing. Given that the peaks usually occur at different times, multiple peaks in this and similar studies are frequently not apparent in graphical summaries of the mean concentrations. In this study, multiple peaks were detected in the plasma prochlorperazine concentration profiles, both after intravenous administration and after inhalational prochlorperazine administration. Others have noted a “somewhat erratic initial ‘distribution’ phase” following a 20 min intravenous prochlorperazine infusion to patients, but they have not attempted to characterize it.¹² Multiple plasma concentration peaks after nonintravenous drug administration have been characterized by multiportion absorption models, including parallel first-order absorption models and discontinuous first-order absorption models.¹⁸ In this study, the multiple plasma concentration peaks, detected both after intravenous administration and after aerosol administration, have been simultaneously characterized as representing multiportion absorption, using three parallel absorption

delay elements. The observation of multiple plasma concentration peaks after each of the methods of administration of prochlorperazine confirms that the multiportion absorption is similar for both routes of administration. Potential explanations of the multiple peaks in plasma prochlorperazine concentrations after either route include elution from the lungs (and, possibly, from other tissues) after extensive first-pass pulmonary (and, possibly, other tissue) uptake,^{19,20} mobilization of drug from tissues by suddenly increased cardiac output or suddenly altered cardiac output distribution,²¹ and enterohepatic recirculation.²²

Prochlorperazine is a highly lipophilic ($\log P = 4.79$) basic amine ($pK_a = 8.21$).²³ When a lipophilic basic amine with a pK_a value larger than 8 is rapidly introduced into the circulation, as by rapid intravenous infusion, the lungs affect the drug’s arterial concentration vs. time relationship because of its extensive partitioning into pulmonary tissue.^{19,20} The volume of distribution of the basic amine fentanyl in pulmonary vascular endothelial cells is 60 times that of antipyrine, which is a marker of total body water.²⁴ The lung:blood concentration ratio of the basic amine imipramine is 61 times higher than that of antipyrine at 2 min after intravenous administration to rats and 124 times higher after 60 min.²⁵ Extensive pulmonary drug distribution results in an increased pulmonary MTT for the drug on first pass, decreased peak arterial drug concentrations, and slow release from lung tissue as blood concentrations fall below those in the lungs. Multiple pools of basic amine distribution into lungs are suggested by studies of both uptake and efflux and are represented by membrane binding and lysosomal trapping.²⁶ Pulmonary uptake of lipophilic basic amines consists of both a passive diffusion process and a saturable process, not only in cultured pulmonary vascular endothelial cells but also in isolated perfused lungs.^{24,27,28} Fast-, medium-, and slow-eluting pools of basic amines have been identified in isolated perfused lung preparations, with elution from drug pools in the lung taking place with half-lives ranging from seconds to hours.^{27,28} Although it has apparently not been formally studied, prochlorperazine pulmonary uptake is probably as extensive as that of its phenothiazine analog, chlorpromazine.²⁹ Multiple plasma concentration peaks after both rapid intravenous administration and inhalational administration could be consistent with multiportion prochlorperazine elution from the lung (and, possibly, from other tissues).

Cardiac output and its distribution can affect drug disposition. In a crossover study of human volunteers, pseudo steady-state propranolol concentrations of 30 ng/ml doubled the area under the antipyrine concentration vs. time curve for at least the first 3 min after injection, both by decreasing the cardiac output and by maintaining nondistributive blood flow at the expense of a reduced blood flow to the rapidly equilibrating tissue volume.³⁰ Two dogs recovering from anesthesia that had been induced and maintained for 6 h by a methohexital infusion showed sudden increases in plasma methohexital concentrations when convulsing while recovering from anesthesia, and four of five dogs studied had increases in plasma methohexital concentrations upon attaining sternal recumbency, presumably as a result of changes in cardiac output and regional blood flow during

recovery from anesthesia.²¹ The possibility exists that a change in the physiologic status of the subjects in this study occurring at the same time relative to the administration of the two doses of prochlorperazine, associated with activities such as eating or using a restroom, resulted in a change in cardiac output and its distribution and mobilized a large amount of this extensively distributed drug.

In enterohepatic recycling, a drug (or its conjugate) is removed from blood by the hepatocytes, secreted into the bile, deposited into the intestinal lumen, and reabsorbed (after hydrolysis of the conjugate if it had been excreted in that form).²² Enterohepatic recycling can produce multiple peaks in the plasma drug concentration vs. time relationship at irregular intervals owing to gallbladder emptying as food is digested in the upper gastrointestinal tract. The secondary peaks resulting from gallbladder emptying can be described by delay times such as those of the model in this study.³¹ However, enterohepatic recycling of prochlorperazine is considered unlikely, because its molecular weight (373.94) is considerably less than the molecular weight threshold for enterohepatic recycling in humans (500–600). Also, because it is a high-clearance drug, little of the drug that is deposited into the intestinal lumen during the recycling process is likely to survive absorption from it.

Administration of TGA prochlorperazine to volunteers by single-breath inhalation resulted in drug pharmacokinetics similar in terms of speed, extent, and consistency of absorption to that observed after intravenous administration. The observation of multiple peaks in plasma prochlorperazine concentrations after rapid systemic administration, whether intravenously or by inhalation, suggests that these peaks are a characteristic of the drug rather than of the mode of administration and may reflect multipoint prochlorperazine elution from the lung following first-pass pulmonary uptake. The results of our study suggest that pulmonary administration via a properly designed TGA may offer a viable alternative to rapid intravenous administration of prochlorperazine for the treatment of an acute migraine attack and also for administering other drugs in situations that require fast, predictable production of effective plasma concentrations.

METHODS

Subjects and study design. Eight normal, healthy adult volunteers participated in this two-period crossover study of the pharmacokinetics of prochlorperazine administered intravenously or by inhalation, which was conducted by PPD (Austin, TX). Male and female volunteers who were between 18 and 45 years of age, free of tobacco and drug use, in good general health and of normal weight, not pregnant, and proficient in English were eligible to participate in this study. Six male volunteers and two female volunteers of median body weight 72.5 kg (range 60.6–85.2 kg) and median age 29.5 years (range 21–45 years) were included in this study after providing institutional review board–approved, written informed consent.

The order of treatment (intravenous administration or inhalation administration) was randomized as determined by computer-generated randomization. For each volunteer, a coated dose of 0.625 mg (0.5 mg emitted dose) of prochlorperazine was administered as a TGA by single-breath inhalation via the Staccato system delivery platform (Alexza Pharmaceuticals, Mountain View, CA)^{9–11} in one session, and 0.5 mg of prochlorperazine was administered as a 5-s intravenous infusion through an indwelling venous forearm catheter in the other session. Washout

periods of at least 5 days were required between dosing days. The doses administered were based on *in vitro* studies indicating that the dose emitted as a TGA is 80% of the coated dose.¹⁰

Blood samples were drawn using peripheral venous access, either via an indwelling catheter or by direct venipuncture from the arm opposite that used for intravenous prochlorperazine administration. Seven milliliters of blood were withdrawn to provide plasma for drug concentration measurements before drug administration and at 1, 2, 3, 5, 10, 15, 20, 30, and 45 min and at 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h after beginning drug administration. The blood samples were transferred to tubes containing EDTA and centrifuged, and the plasma was collected and frozen awaiting assay for prochlorperazine concentrations.

Analytical methods. Plasma prochlorperazine concentrations were measured by PHARMout Laboratories (Sunnyvale, CA), using liquid chromatography–tandem mass spectrometry on samples prepared by solid-phase extraction.

In brief, 50 μ l of 50 ng/ml ²H₃-prochlorperazine (internal standard) solution was mixed with 250 μ l of plasma samples diluted 1:3 with water and applied to conditioned 30 mg CN solid-phase extraction columns, from which they were eluted with 750 μ l of acetonitrile after water and methanol washes. Eluants were diluted 1:2 with 2 mmol/l ammonium acetate buffer, pH 4.0–5.0, and analyzed using an API 4000 liquid chromatography–tandem mass spectrometry system (Applied Biosystems, Foster City, CA) equipped with a SIL-10 AXL HPLC autosampler and LC-10AD HPLC pump (Shimadzu Scientific Instruments, Pleasanton, CA). The samples were subjected to isocratic elution from a Synergi 4 μ m Fusion-RP 80A column (50 \times 2.0 mm, Phenomenex, Torrance, CA), with a mobile phase consisting of 28% acetonitrile, 32% methanol, 0.1% formic acid, and 0.2% 1.0 mol/l ammonium acetate buffer, pH 4.0–5.0, balanced with water, at a flow rate of 0.2–0.3 ml/min. The turbo-ion-spray source of the tandem mass spectrometer was operated in the positive ionization mode. The mass-to-charge ratios of the precursor-to-product ion reaction monitored for prochlorperazine were 374.00 \rightarrow 141.20. Drug concentrations were calculated by comparing prochlorperazine/internal standard ratios to a standard curve (0.1–50 ng/ml prochlorperazine) prepared in blank human plasma. The prochlorperazine retention time was <5 min. The lower limit of quantitation of the plasma prochlorperazine assay was 0.1 ng/ml. For low, medium, and high quality control samples (0.20, 20.0, and 40.0 ng/ml, respectively), intra-assay coefficients of variation ranged from 1.01 to 10.2%, whereas interassay coefficients of variation ranged from 1.90 to 8.65%. At the lower limit of quantitation (0.1 ng/ml), intra-assay coefficients of variation ranged from 3.27 to 9.35%, whereas the interassay coefficient of variation was 9.27%.

Pharmacokinetic model. Plasma prochlorperazine concentration vs. time relationships were modeled using the SAAM II software system (SAAM Institute, Seattle, WA) implemented on a Windows-based PC. Plasma drug concentrations were characterized in terms of a two-compartment pharmacokinetic model (Figure 1). Drug absorption was described using tanks-in-series delay elements (represented by rectangles with two cells) to characterize the noninstantaneous appearance of the drug in the body. The absorption fraction, F_{in} , determined the fraction of the drug absorbed (bioavailability); the rate of absorption was characterized by the delay element and the associated MTT (described below). The SAAM II objective function used was the extended least-squares maximum likelihood function using data weighted with the inverse of the model-based variance of the data at the observation time points.³² Systematic deviations of observed data from the calculated values were sought, using the one-tailed one-sample runs test (results not shown), with $P < 0.05$ —corrected for multiple applications of the runs test—as the criterion for rejection of the null hypothesis. Model misspecification was sought by visual inspection of the measured and predicted drug concentrations vs. time relationships. The appropriateness of the choice of model was evaluated using the Akaike information criterion and the Schwarz-Bayesian information criterion.^{33,34}

As mentioned earlier, the single absorption delay element model (Figure 1) developed to describe prochlorperazine disposition after both TGA administration and intravenous administration of the drug in dogs¹¹ could not be fitted to the multiple peaks observed after prochlorperazine administration to human volunteers (Figure 2). Therefore, we first developed a pharmacokinetic model that described the disposition of the inhaled dose in humans. Subsequently, the model developed for the inhaled dose was used to model the data collected after the crossover aerosol drug administration and 5-s intravenous drug administration, simultaneously for each subject.

Simultaneous estimation of pharmacokinetic parameters for both intravenous and aerosol routes of administration permitted calculation of the bioavailability of the emitted prochlorperazine aerosol dose, F_{Aero} (Figure 1). For the combined model of the intravenously administered dose and the inhaled (i.e., aerosol) dose to have the same volumes and clearances without systematic errors in the fit of the two simultaneously modeled data sets, the aerosol dose had to be corrected for any portion of the drug not reaching the central compartment. The modeling program did this by adjusting k_{in} (and k_{out}) so that the $AUC_{0 \rightarrow \infty}$ of the plasma drug concentration histories were consistent with the administered doses (i.e., $F_{Aero} \text{Dose}_{Aero} / AUC_{Aero 0 \rightarrow \infty} = \text{Dose}_{IV} / AUC_{IV 0 \rightarrow \infty}$).

MTTs for each tanks-in-series absorption delay element were calculated from the number of cells in a delay element, n , and the rate constant exiting each cell, k :

$$MTT = \frac{n}{k} \quad (1)$$

The percentage of the dose absorbed through each absorption delay element (percentage of dose absorbed) was calculated as the fraction of the sum of all absorption rate constants represented by each of the individual rate constants.

Descriptive statistics. Data are expressed as mean \pm SD, or geometric mean and 95% confidence interval. Within-subject differences in initial peak concentrations and times were assessed using the paired t -test, with $P < 0.05$.

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CONFLICT OF INTEREST

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