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Pharmacokinetics of Dopamine in Healthy Male Subjects

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Background: **Dopamine is an agonist of α, β, and dopaminergic receptors with varying hemodynamic effects depending on the dose of drug being administered. The purpose of this study was to measure plasma concentrations of dopamine in a homogeneous group of healthy male subjects to develop a pharmacokinetic model for the drug. Our hypothesis was that dopamine concentrations can be predicted from the infusion dose using a population-based pharmacokinetic model.**

Methods: **Nine healthy male volunteers aged 23 to 45 yr were studied in a clinical research facility within our academic medical center. After placement of venous and arterial catheters, dopamine was infused at 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 10 min, followed by a 30-min washout period. Subsequently, dopamine was infused at 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 90 min, followed by another 30-min washout period. Timed arterial blood samples were centrifuged, and the plasma was analyzed by high-performance liquid chromatography. Mixed-effects pharmacokinetic models using NONMEM software (NONMEM Project Group, University of California, San Francisco, CA) were used to determine the optimal compartmental pharmacokinetic model for dopamine.**

Results: **Plasma concentrations of dopamine varied from 12,300 to 201,500 ng/l after 10 min of dopamine infusion at 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Similarly, steady-state dopamine concentrations varied from 1,880 to 18,300 ng/l in these same subjects receiving 3-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusions for 90 min. A two-compartment model adjusted for body weight was the best model based on the Schwartz-Bayesian criterion.**

Conclusions: **Despite a homogeneous population of healthy male subjects and weight-based dosing, there was 10- to 75-fold intersubject variability in plasma dopamine concentrations, making standard pharmacokinetic modeling of less utility than for other drugs. The data suggest marked intraindividual and interindividual variability in dopamine distribution and/or metabolism. Thus, plasma dopamine concentrations in patients receiving dopamine infusion at identical rates may vary profoundly. Our data suggest that dosing dopamine based on body weight does not yield predictable blood concentrations. (Key words: Catecholamines; clearance; drug dosing; half-life; inotropes.)**

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DOPAMINE is an endogenous catecholamine that regulates cardiac, vascular, and endocrine function. Dopamine is also used clinically to support organ function and to modulate hemodynamics in critically ill patients. Conventional teaching[1] states that when exogenous dopamine is infused at low doses (between 0.5 and 3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$), the predominate effects are stimulation of dopaminergic receptors with resultant increases in splanchnic (including renal) blood flow, diuresis, and natriuresis. At higher doses (> 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$), β-adrenergic receptor stimulation predominates, increasing cardiac inotropy and chronotropy. Doses > 7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ result in predominate α-adrenergic stimulation, resulting in peripheral and splanchnic vasoconstriction. Despite this conventional wisdom, clinical experience demonstrates that there is considerable interpatient variability in response to dopamine infusions, even when administered at identical rates.

The purpose of this study was to define the pharmacokinetics of dopamine infusions in a homogeneous

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Table 1. Timing of Blood Samples and Heart Rate Measurements during the Four Phases of the Study

Sample Number	Dopamine (10 $\mu g \cdot kg^{-1} \cdot min^{-1}$)	First Washout Period	Dopamine (3 $\mu g \cdot kg^{-1} \cdot min^{-1}$)	Second Washout Period
1	30 s	30 s	30 s	30 s
2	1 min	1 min	1 min	1 min
3	2 min	2 min	2 min	2 min
4	4 min	4 min	5 min	4 min
5	7 min*	7 min	10 min	7 min
6	10 min*	10 min	30 min*	10 min
7		15 min	60 min*	15 min
8		20 min*	90 min*	20 min*
9		30 min*		30 min*

* Time points for values displayed in Figure 2. Blood samples were drawn into evacuated blood collection tubes beginning precisely at the above listed times.

group of healthy male subjects. Our goal was to classify dopamine into either a one-, two-, or three-compartment model and to derive the kinetic parameters of clearance, volume of distribution, and terminal half-life. Our hypothesis was that a pharmacokinetic model of dopamine could be used to define doses of the drug that would be required to obtain specific plasma concentrations.

Methods

This study was reviewed and approved by the Institutional Review Board of Wake Forest University Baptist Medical Center. Informed consent was obtained from nine healthy, nonobese male volunteers between the ages of 23 and 45 years who were compensated for their time. Healthy, young-adult, male volunteers were selected as the study population to minimize demographic variability between subjects. Specifically, our goal was to minimize the effects of sex hormones, extremes of age and weight, and organ dysfunction. We planned to study 10 subjects, but 1 subject unexpectedly withdrew, and we were unable to schedule a replacement while we had research space and staff to complete the study.

An intravenous catheter was placed in each volunteer's dominant arm, and an arterial catheter was placed in the opposite radial artery. Monitors consisted of electrocardiogram, pulse oximeter, and noninvasive blood pressure cuff. Serum electrolyte and creatinine concentrations were measured for each volunteer. Once heart rate and blood pressure had remained unchanged for a period of 10 min, a continuous infusion of dopamine at 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was begun and continued for 10 min. After discontinuing the infusion, a 30-min washout period was observed. At the conclusion of this washout period, dopamine infusion was restarted at 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and continued for 90 min. Another 30-min washout period was observed after the 3-$\mu g \cdot kg^{-1} \cdot min^{-1}$ dopamine infusion was discontinued. Heart rate and blood pressure were monitored during each phase of the study.

Table 1 details the timing of 32 blood samples obtained from each subject. Evacuated blood collection tubes were used to withdraw blood, with 3 ml of blood removed 5 s before the stated collection times, and a 3-ml sample withdrawn beginning precisely at the listed times. Blood samples drawn from the catheter were immediately placed on ice. During each washout phase and immediately after completion of each phase of the study (*i.e.*, within 20 min for each sample), samples were centrifuged, the pellet was discarded, and the plasma was removed and frozen at −70°C. Plasma samples were thawed, and dopamine concentrations were analyzed after alumina extraction by high-performance liquid chromatogaphy and electrochemical detection as previously described.[2] Absolute detection limit was 0.8 ng/l. Interval reference standards were mixed randomly with subjects' samples to confirm the ongoing accuracy and precision of the assays; interassay coefficient of variation at 10 ng/l was 4.6%.

Statistical Methods

Concentration-*versus*-time data were fit to several variations of one-, two-, and three-compartment models with and without absorption lags and rates. Population models were fit using nonlinear mixed-effects regression techniques with the NONMEM software package (NONMEM Project Group, University of California, San Francisco, CA). NONMEM fits models by minimizing the $-2 \times$ log likelihood objective function as it simultaneously estimates the model's pharmacokinetic parameters, their interindividual variance, and the intraindividual residual variability (the mixed-effects approach).

This objective function minimization was achieved using NONMEM's Laplacian method, an algorithm using second-order derivatives. In addition to the aforementioned population modeling, NONMEM was used to fit models to each individual patient separately (the interindividual variance parameters being excluded). The parameter estimates from each individual were then combined using geometric means (the two-stage approach). In an attempt to maximize the precision of our models, parameter covariates of age, sex, weight, and serum creatinine were included in some of the models tested. Models were judged best that simultaneously minimized both the $-2 \times$ log likelihood objective function and number of model parameters, as indicated by the Schwartz-Bayesian criterion. Selection was further aided by the graphic examination of the model fits and residual plots. Model microrate constants, k_{10}, k_{12}, k_{21}, k_{13}, and k_{31}, and the central compartment's volume of distribution, V_1, were estimated directly by the NONMEM program. Clearances (Cl) and the remaining compartment volumes of distribution were calculated from the rate constants as follows:

$$Cl_{10} = V_1 \cdot k_{10},\ Cl_{12} = V_1 \cdot k_{12},\ \text{and}\ V_2 = k_{12} \cdot V_1/k_{21} \quad (1)$$

Parameter subscripts refer to the model's compartment number. Double subscripts refer to flow from one compartment to the next (*e.g.*, k_{12} is the rate constant describing drug movement from compartment 1 to compartment 2). Compartment 0 is outside the body (*i.e.*, k_{10} is the rate constant describing drug elimination). Exponential coefficients and half-lives were calculated using standard equations.

For two-compartment models, steady-state concentrations (C_{ss}) during continuous infusions were calculated as follows[3]:

$$C_{ss} = k_0 \cdot k_{21}/(V_1 \cdot \alpha \cdot \beta) \quad (2)$$

where k_0 is the infusion rate constant, α is the initial exponential rate constant from biexponential disposition model, and β is the terminal exponential rate constant from biexponential disposition model.

The possible effects of sex, age, weight, and creatinine clearance on C_{ss} were tested using linear and loglinear regression. The mixed-effects interpatient variability of the rate constants and V_1 were modeled lognormal in distribution. Models of intraindividual residual variability fit by NONMEM included the constant coefficient of variability model, the combined additive and constant coefficient of variability model, and the power function model.

Table 2. Demographics of the Nine Volunteer Subjects

Subject	Age (yr)	Height (cm)	Weight (kg)	Creatinine (mg/dl)
1	39	171	75	0.9
2	29	177	91	0.9
3	39	166	85	1.1
4	26	166	73	0.9
5	34	178	93	1.0
6	45	171	84	0.8
7	36	186	108	0.8
8	23	181	116	1.0
9	25	176	82	0.8
Mean	33	175	90	0.9

Simple measures of model performance were calculated, including absolute performance error (APE). APE calculations were made for each individual, modified from procedures described by Coetzee *et al.*,[4] as follows:

$$APE_{ij} = |(obs_{ij} - pred_{ij})|/pred_{ij}$$

where obs is the observed (measured) concentration; pred is the predicted concentration from the model; and the subscripts i and j refer to the jth time of the ith individual.

With these calculations, APE_{50} is the median APE_{ij} over the entire range of i and j, and APE_{95} is the 95th percentile APE_{ij}. The APE_{50} and APE_{95} are based on the absolute values and represent the ranges within which 50% or 95% of the APE occur.

Repeated measured analysis of variance tested for heart rate changes between baseline, the 10-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion peak, the first washout, the 3-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion peak, and the second washout period. This analysis of variance was performed using the Proc Mixed subroutines of SAS version 6.12 (SAS Institute, Inc., Cary, NC).

Results

The demographics of our nine subjects are listed in table 2. The body mass index [weight in kilograms/(height in meters)^2] ranged from 25.6 to 35.4 with a mean $\pm$ SD of 29.2 $\pm$ 3.0. Dopamine concentrations for all subjects and time points are illustrated in figure 1. There was a total of nine missing data points because of sampling errors. One of these errors occurred during the initial baseline phase, and another (different subject) occurred during the final washout phase. There were no other technical errors during the study or during measurement of plasma concentrations.

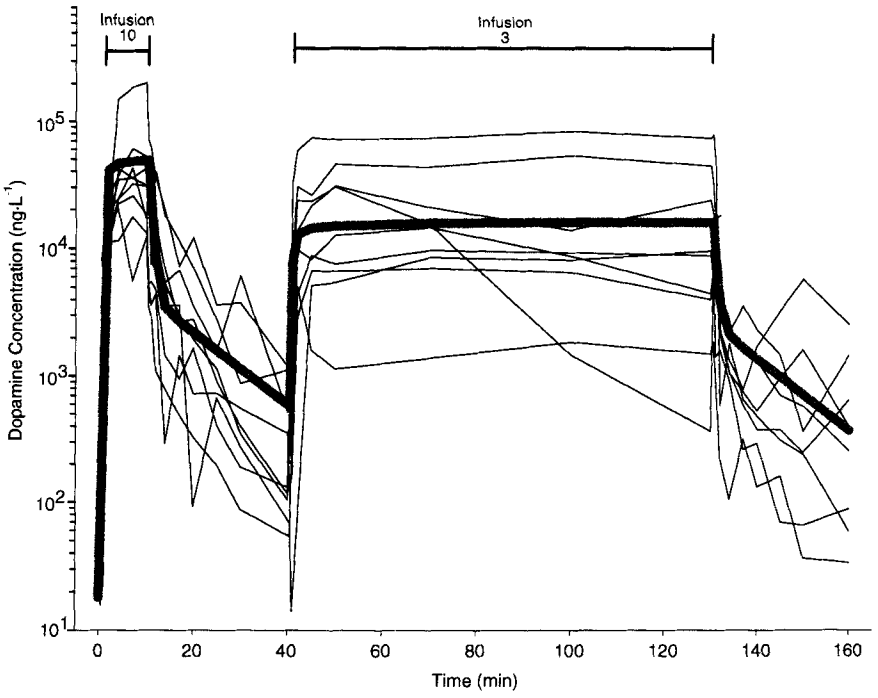

Fig. 1. Dopamine plasma concentrations. Log scale dopamine plasma concentrations for each measurement on each of the nine volunteers. Infusion 10 represents the 10-μ · kg^{-1} · min^{-1} dose that was infused from 0 to 10 min. Infusion 3 represents the 3-μ · kg^{-1} · min^{-1} dose that was infused from 40 to 130 min. The gray-shadowed bar represents the best fit predicted curve as determined by the pharmacokinetic model (see text).

Initial basal dopamine plasma concentrations varied over a wide range from 3 to 8,023 ng/l. These concentrations were not significantly different from those measured at the end of the two subsequent washout periods (fig. 2, top), and there was no correlation between basal dopamine concentrations and weight. After initiation of the 10-μg · kg^{-1} · min^{-1} infusion (10 min), plasma concentrations increased rapidly, with individual plasma concentrations for the 7- and 10-min samples ranging from 5,616 to 201,513 ng/l. After termination of the 10-min bolus infusions, dopamine concentrations decreased rapidly, ranging from undetectable to 1,191 ng/l. Dopamine concentrations during the 90-min infusion at 3 μg · kg^{-1} · min^{-1} appeared to reach a steady-state plateau rapidly, with individual measurements of plasma concentrations varying between 367 to 83,745 ng/l. After termination of the infusion, dopamine plasma concentrations decreased precipitously back to baseline levels. Figure 2 (top) demonstrates the concentrations obtained during the final two measurements (7 and 10 min) during the 10-μg · kg^{-1} · min^{-1} infusion and the final three measurements (30, 60, and 90 min) during the 3-μg · kg^{-1} · min^{-1} infusions, as well as the interceding baseline values. Of note, the subjects with the highest baseline concentrations did not have the highest concentrations during the drug infusions, and many of the washout concentrations were lower than the original baseline concentrations for the same subjects.

The mixed-effects population models best fit the data to a two-compartment model with an absorption lag of 0.5 min and V_1 adjusted for body weight. This best model characterized the interindividual variability as lognormal in distribution and modeled the intraindividual residual error using a constant coefficient of variability model (constant coefficient of variability, residual error = $\sigma_1 \times$ predicted outcome). Selection criteria for a representative four of our tested models are listed in table 3. This table is not inclusive of all the mixed-effects models tested but demonstrates the process of building what ultimately became the best fit model (model D). This best fit model performs best using the Schwartz-Bayesian criterion.

The best model is characterized by its extremely rapid microrate constants (k_{10} = 1.10, k_{12} = 0.244, and k_{21} = 0.07), resulting in an initial half-life, $t_{1/2,\alpha}$ = 0.5 min, a systemic clearance (Cl_1) equal to 110% of the central compartment's volume of distribution (V_1) per minute, and a terminal half-life, $t_{1/2,\beta}$ = 12.3 min (table 4). These rapid rates agree with the immediate increase and decrease of dopamine concentrations before and after infusion (fig. 1). Dopamine C_{ss} (in ng · l^{-1} · kg^{-1}) during any prolonged continuous infusion can be estimated from equation 2 and our model as:

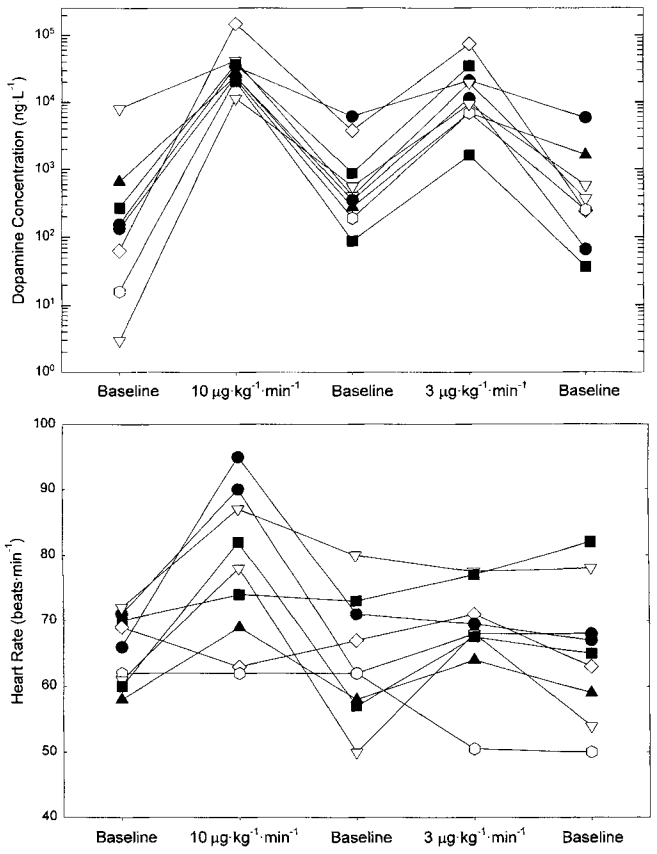

Fig. 2. Dopamine concentrations and heart rates. Data for the dopamine concentrations (*top*) are presented for the initial baseline concentrations, the average concentrations measured from the 7- and 10-min samples during the 10-$\mu \cdot kg^{-1} \cdot min^{-1}$ dose, the concentrations measured at the end of the first washout period, the average concentrations measured from the 30-, 60-, and 90-min samples during the 3-$\mu \cdot kg^{-1} \cdot min^{-1}$ dose, and the concentrations measured at the end of the final washout period. Heart rate data (*bottom*) were recorded at the initial baseline, 8 min into the 10-$\mu \cdot kg^{-1} \cdot min^{-1}$ dose, at the end of the first washout period, 45 min into the 3-$\mu \cdot kg^{-1} \cdot min^{-1}$ dose, and at the end of the final washout period.

$$C_{ss} = (3.77 \text{ min/l}) \cdot k_0 \cdot 1{,}000 \quad (3)$$

where k_0 is the infusion rate (in $\mu g \cdot kg^{-1} \cdot min^{-1}$), and 1,000 corrects the dose units (μg) to concentration units (ng).

This equation estimates C_{ss} for 3- and 10-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusions at 11,300 and 37,700 ng $\cdot kg^{-1} \cdot l^{-1}$, respectively. These concentrations at steady state (C_{ss}) are asymptotes; C_{ss} is only reached as time approaches infinity. However, based on simulations using our model, dopamine concentrations during continuous infusion will reach 88.9% of C_{ss} at 10 min, 90% of C_{ss} at 12.3 min, and 95% of C_{ss} at 24.8 min. This best model uses a weight-adjusted infusion rate, but there were no significant effects of patient age, sex, or serum creatinine on C_{ss}.

Our best model outperforms all other models using the Schwartz-Bayesian criterion as well as two other commonly used indices of selection criteria, the $-2 \cdot$ log [likelihood] and the Akaike Information Criterion. Using this best model, the APE_{50} and APE_{95} were 59% and 514%, respectively. These performance measures can be interpreted as 50% of our measured concentrations differ from predicted concentration by no more than 59%, whereas 95% of measured concentrations differ from model predictions by no more than 514% of the predicted concentrations. Graphical representation of our best fit pharmacokinetic model is included in figure 1 as the shaded curve.

The best fit two-stage modeling approach resulted in a one-compartment model with no lag time (k_{10} = 0.44 min^{-1} and V_1 = 55.5 l) and had an overall APE_{50} of 81% and APE_{95} > 100,000%. The two-stage model fits were far inferior to our best mixed-effects models and thus are not mentioned further.

Table 5 demonstrates the performance characteristics of our best mixed-effects fit model by individual subject. This table demonstrates that for five of the nine subjects, the curve fit very well (APE_{95} < 100%), whereas four subjects varied from the predicted values by considerable amounts (APE_{95} from 194% to 648%). Additional parameter adjustments for the demographic covariates of age, weight, or serum creatinine could not account for this subject-to-subject variability.

Figure 2 (bottom) displays the heart rates measured during the initial baseline; 8 min into the 10-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion; 25 min into the first washout period; 45 min into the 3-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion; and at the end of the final washout period. Heart rate was monitored as a safety issue rather than a therapeutic end point. Repeated measures analysis of variance found no differences between the heart rates for the three baselines. Mean heart rate increased significantly with the infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ but did not increase above baseline with the prolonged infusion of 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$.

Discussion

Most studies of drug pharmacokinetics assume a single compartment into which the drug is administered, commonly represented by plasma volume, and that there is

Table 3. Pharmacokinetic Model Selection Criteria for Four Illustrative Model Fits

Model	A	B	C	D	
Compartments	1	2	2	2	
Absorption lag	No	No	Yes	Yes	
Covariates	No	No	No	Weight-adjusted V_1	
Residual error structure	Combined additive and CCV	Combined additive and CCV	Combined additive and CCV	CCV	
Parameters estimated	6	10	11	10	
Model selection criteria					
−2LL (smaller is better)	1326.86	1224.48	1150.44	1088.10 (best)	
SBC (larger is better)	−680.08	−639.98	−605.74	−571.80 (best)	
AIC (larger is better)	−669.43	−622.24	−586.22	−554.05 (best)	
LRT (P value)	—	<0.0001	<0.0001	—	
Standard error estimates	Yes	Yes	No	Yes	
Overall model performance					One-compartment Two-stage
APE_{50}	±78%	±62%	±55%	±59%	±81%
APE_{95}	±100,000%	±600%	±737%	±514%	±186,741%

CCV = constant coefficient of variability model; SBC = Schwartz-Bayesian Criterion; AIC = Akaike's Information Criterion; LRT (P value) = P values from the Likelihood Ratio Test, which can only be used to compare nested models. These P-values compare the model with the model immediately to its left.

−2LL = −2 · log (likelihood) is the objective function minimized by NONMEM during model fitting of parameter estimates. −2LL, AIC and LRT (P value) are included for readers more familiar with these model selection criteria. SBC is the most parsimonious in adding model parameters and thus our basis for model selection.

no other source of drug within the body. The elimination of drug from this single compartment is dependent on clearance of the drug out of the plasma either by excretion from the body or through terminal metabolism. Our study modeled the pharmacokinetics of dopamine in healthy male subjects receiving clinically relevant doses of dopamine infusions at 10 and 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ using compartmental models. Compartmental pharmacokinetic models are based on the assumption that the concentration at any time is directly proportional to the infusion dosages. This assumption of linearity would suggest that for a given dosing scheme, tripling the amount of drug infused will triple the expected drug concentrations at any given sampling time.

Rarely do drugs actually follow such a simplified kinetic scheme; most drugs are better described by a more complex exponential model, thus accounting for alterations in drug concentration that result from redistribution of drug into a second "peripheral" compartment from which it can distribute back into the plasma "central" compartment. Multiexponential models describing the pharmacokinetics of drugs with more than a single compartment have been described for a number of medications, including narcotics, inotropic medications, benzodiazepines, and other anesthetic drugs.[4-11] Defining the pharmacokinetic parameters for a drug allows for more precise determination of dosing to accommodate changes in drug distribution associated with physiologic parameters such as age, gender, and body weight, as well as changes brought about by disease states and organ dysfunction.[5,7,12-15] Many of these pharmacokinetic studies have raised doubt about using body weight as the primary adjustment for dosing drugs, a conflict recently highlighted by Bouillon and Shafer.[16]

Dopamine is known to increase cardiac output, which, in turn, may affect its own clearance. Thus, rates of clearance and other pharmacokinetic parameters may change as plasma dopamine concentrations change. Such dose and concentration-dependent changes in pharmacokinetic parameters would violate pharmacokinetic linearity and may account for our model predictions (fig. 1) overestimating plasma concentrations during the 10-min infusion. Nonlinearity may also explain why "renal dose" dopamine (3.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) infusions result in plasma concentrations equivalent to plasma concentrations achieved with 10-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusions. Any concentration-dependent changes in the pharmacokinetic parameters would violate the assumption of linearity and question the validity of compartmental models.

Regardless of nonlinear pharmacokinetics and other possible model misspecifications, our two-compartment model predictions do, for the most part, follow the median observed dopamine concentrations (fig. 1). Indi-

Table 4. Pharmacokinetic Parameter Estimates for Our Best Model

Fitted Parameters	Estimate ± Standard Error	Units
Micro-Rate Constants		
Lag	0.508 ± 0.002	(min)
k_{12}	0.244 ± 0.054	(min^{-1})
k_{21}	0.070 ± 0.018	(min^{-1})
k_{10}	1.10 ± 0.11	(min^{-1})
V_1	0.241 ± 0.087	($l \cdot kg^{-1}$)*
Derived Alternate Parameters		
Clearance/volumes		
Cl_{10}	0.27	$l \cdot kg^{-1} \cdot min^{-1}$
Cl_{12}, Cl_{21}	0.059	$l \cdot kg^{-1} \cdot min^{-1}$
V_2	0.840	$l \cdot kg^{-1}$
Biexponential		
A	4.11 · (dose)†	$\mu g \cdot l^{-1} \cdot kg^{-1}$
B	0.0423 · (dose)	$\mu g \cdot l^{-1} \cdot kg^{-1}$
α	1.36	min^{-1}
β	0.0567	min^{-1}
Half-lives		
$t_{1/2\alpha}$	0.511	min
$t_{1/2\beta}$	12.3	min
Estimate time to within		
90% of C_{ss}‡	12.3	min
95% of C_{ss}	24.8	min

* Parameters with kg^{-1} unit are weight-adjusted; per kg of body weight; † Dose is body weight-adjusted as $\mu g \cdot kg^{-1}$; ‡ Concentration at theoretical steady-state reached during a prolonged continuous infusion.

vidual measurements of plasma dopamine concentrations do, however, vary as much as 75-fold, despite the use of identical weight-based infusion rates. The random plasma concentration peaks observed at lower concentrations during the postinfusion sample times may reflect experimental error or system instability caused by the influences of endogenous dopamine concentrations. Such large variability in plasma concentrations in a homogeneous population of healthy male subjects casts doubt on the reliability of using any pharmacokinetic model to predict plasma concentrations.

Study designs for determining drug pharmacokinetics involve starting and stopping the drug and measuring concentrations frequently as the changes in plasma concentration occur. Ideally, the drug could be administered in doses less than, equivalent to, and greater than standard clinical practices to define the upper and lower limits of plasma concentrations and pharmacokinetic variables. Our design began with a group of healthy male volunteers to limit demographic differences and to use a moderately high dose (10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) but to limit the duration of this infusion to avoid unpleasant side effects encountered in previous studies we conducted with the drug. Thus, 10 min was chosen for the higher dose, then a prolonged infusion with the better-tolerated 3-$\mu g \cdot kg^{-1} \cdot min^{-1}$ dose. We prospectively chose not to randomize this order because we felt a prolonged infusion was more likely to cause accumulation of drug, and a longer washout phase would be required. Given the rapidity of washout of the drug, this assumption seems to have been incorrect, and dose randomization could have been performed. Our design leaves open the potential that sequential dosing effects have influenced our results.

Previous studies have measured endogenous catecholamine levels under different physiologic conditions. Regitz *et al.*[17] demonstrated large variability in dopamine (and other catecholamines) in healthy control subjects. Schwartz *et al.*[18] demonstrated variations in dopamine concentrations at rest and during angina. Zaloga *et al.*[19] reported a wide range of epinephrine concentrations after coronary artery bypass grafting. In this same study, dopamine concentrations were also measured but were not reported because of the tremendous variability in the measured concentrations (personal communication from the authors, September 1998). These wide variations are confirmed by the baseline values we measured, and the large intrapatient variability is confirmed by the fact that the concentrations measured during the washout phases were lower than baseline concentrations for some of our subjects. It remains unclear how much of the discrepancies in plasma concentrations are cause by endogenous dopamine, initial distribution, compartmental differentiation between subjects, genetic differences in catecholamine metabolism, or dopamine-induced changes in metabolism of the drug. Regardless of the cause of these intrapatient and interpatient differences, our data demonstrate that plasma dopamine concentrations in subjects receiving "renal dose" dopamine at 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ may actually exceed plasma concentrations in other subjects receiving 10-$\mu g \cdot kg^{-1} \cdot min^{-1}$

Table 5. Performance Errors by Individual Study

ID	APE_{50i} (%)	APE_{95i} (%
1	36	509
2	43	194
3	158	475
4	319	648
5	39	100
6	56	84
7	46	90
8	35	84
9	85	94

infusions. This phenomenon occurred in our study, with four subjects having peak plasma concentrations during the 10-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusions that were lower than maximal concentrations achieved by four other subjects during the 3-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusions.

Additional studies have attempted to define pharmacokinetic variables for dopamine. Le Corre *et al.*[20] determined that the volume of distribution and clearance of dopamine varied according to the dose of drug infused. This finding suggested nonlinear, dose-dependent pharmacokinetics for the drug and possible receptor or metabolic "saturation." The reported steady-state volumes of distribution were 0.78 ± 0.22 l/kg and 1.58 ± 0.62 l/kg for doses of 3 and 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$, respectively, and these values were similar whether a one- or two-compartment model was used. However, this study was conducted using a small number of patients within the intensive care unit, with varying degrees of organ dysfunction, age, gender, and associated diseases. In a study by Ratge *et al.*,[14] dopamine metabolites were measured using three male and three female volunteers receiving 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of the drug. This study used a single-compartment model to determine the volume of distribution as 2.1 ± 0.5 l/kg. It is unclear if gender had an influence on dopamine pharmacokinetics in this study, but each of these studies demonstrated considerable variability in dopamine concentrations.

The 0.5-min lag time was the most stable model parameter, with a coefficient of variability that was < 1%. The determination of 0.5-min lag time is consistent with the experimental methods; the infusion of drug was intravenous, whereas the sampling of blood was from the arterial catheter. Thus, a short (0.5-min) delay to allow for mixing of samples in the blood stream and circulation of drug to the sampling site is reasonable. A lag is commonly not required for pharmacokinetic modeling when elimination of drug is slower, where the delay is inconsequential. Dopamine concentrations, however, increase and decrease very rapidly, and thus a lag accounts for the rapid shift from low to higher concentrations.

Our study represents the "best case scenario" with little demographic variation between subjects. It is reasonable to assume that had we studied subjects with a wider range of body mass, we would have found even greater variability in pharmacokinetics, as has been demonstrated recently by Egan *et al.*[21] using the opioid remifentanil. Similarly, hormonal influences, age, concomitant administration of medications, and associated disease processes commonly alter the pharmacokinetics of drugs; therefore, extrapolating our predicted concentrations to a population of critically ill patients should be performed with extreme caution. Our study design also does not eliminate the possibility of a drug sequencing effect by starting with a high dose of drug followed by infusion of a lower dose. The likelihood of such a "priming" effect is unlikely given the fact that plasma concentrations decrease back to very low levels (at or below the initial baseline values) between the two drug administrations, and our washout between infusions was of sufficient duration to allow for complete elimination of the drug from the system. In retrospect, however, randomizing the order of infusions would have been appropriate.

There are no published reports that associate the physiologic effects of dopamine with defined plasma concentrations or that determine whether selective stimulation of dopaminergic, β, and α receptors is better accounted for by specific plasma concentrations or by specific infusion rates. Analysis of variance testing showed that heart rate was increased by the higher infusion rate in our study. Nevertheless, we caution that we did not design this study to test for a relationship between dopamine concentrations and clinical effects and can only speculate about the relationship between dopamine concentrations and other clinical variables, such as cardiac output, urine volume, or organ function.

In conclusion, despite designing our study with a homogeneous population of healthy male subjects and using specific weight-based dosing, the plasma concentrations of dopamine we measured varied widely. Although we have been able to construct a pharmacokinetic model of dopamine, the APE for this model remains high. Our data suggest that dopamine dosing based on body weight does not yield consistent, predictable plasma concentrations, even in a population of healthy male subjects.

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References

1. Hoffman BB, Lefkowitz RJ: Catecholamines and sympathomimetic drugs, Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th edition. Edited by Gilman AG, Rall TW, Nies AS, Taylor P. New York, Pergamon Press, 1990, pp 201-2

2. Eisenach JC, Tong C, Limauro D: Intrathecal clonidine and the response to hemorrhage. ANESTHESIOLOGY 1992; 77:522-8

3. Gibaldi M, Perrier D: Pharmacokinetics, 2nd edition. New York. Marcel Dekker, 1982

4. Coetzee JF, Glen JB, Wium CA, Boshoff L: Pharmacokinetics model selection for target controlled infusions of propofol. ANESTHESIOLOGY 1995; 82:1328-45

5. Allen GC, Cattran CB, Peterson RG, Lalande M: Plasma levels of dantrolene following oral administration in malignant hyperthermia-susceptible patients. ANESTHESIOLOGY 1988; 69:900-4

6. Hughes MA, Glass PS, Jacobs JR: Context-sensitive half-time in multicompartment pharmacokinetic models for intravenous anesthetic drugs. ANESTHESIOLOGY 1992; 76:334-41

7. Katz R, Kelly HW: Pharmacokinetics of continuous infusions of fentanyl in critically ill children. Crit Care Med 1993; 21:995-1000

8. Leier CV, Unverferth DV, Kates RE: The relationship between plasma dobutamine concentrations and cardiovascular responses in cardiac failure. Am J Med 1979; 66:238-42

9. Malacrida R, Fritz ME, Suter PM, Crevoisier C: Pharmacokinetics of midazolam administered by continuous intravenous infusion to intensive care patients. Crit Care Med 1992; 20:1123-26

10. Prielipp RC, MacGregor DA, Butterworth JF IV, Meredith JW, Levy JH, Wood KE, Coursin DB: Pharmacodynamics and pharmacokinetics of milrinone administration to increase oxygen delivery in critically ill patients. Chest 1996; 109:1291-301

11. Shafer A, Sung ML, White PF: Pharmacokinetics and pharmacodynamics of alfentanil infusions during general anesthesia. Anesth Analg 1986; 65:1021-8

12. Bush LM, Levison ME: Antibiotic selection and pharmacokinetics in the critically ill. Crit Care Clin 1988; 4:299-324

13. Mackowiak PA: Influence of fever on pharmacokinetics. Rev Infect Dis 1989; 11:804-7

14. Ratge D, Steegmuller U, Mikus G, Kohse KP, Wisser H: Dopamine infusion in healthy subjects and critically ill patients. Clin Exp Pharmacol Physiol 1990; 17:361-9

15. Whipple JK, Ausman RK, Franson T, Quebbeman EJ: Effect of individualized pharmacokinetic dosing on patient outcome. Crit Care Med 1991; 19:1480-5

16. Bouillon T, Shafer SL: Does size matter? ANESTHESIOLOGY 1998; 89:557-60

17. Regitz V, Bossaller C, Strasser R, Schuler S, Hetzer R, Fleck E: Myocardial catecholamine content after heart transplantation. Circulation 1990; 82:620-3

18. Schwartz L, Sole MJ, Vaughan-Neil EF, Hussain NM: Catecholamines in coronary sinus and peripheral plasma during pacing-induced angina in man. Circulation 1979; 59:37-43

19. Zaloga GP, Strickland RA, Butterworth JF IV, Mark LJ, Mills SA, Lake CR: Calcium attenuates epinephrine's beta-adrenergic effects in postoperative heart surgery patients. Circulation 1990; 81:196-200

20. Le Corre P, Malledant Y, Tanguy M, LeVerge R: Steady-state pharmacokinetics of dopamine in adult patients. Crit Care Med 1993; 21:1652-7

21. Egan TD, Huizinga B, Samir K, Gupta SK, Jaarsma RL, Sperry RJ, Yee JB, Muir KT: Remifentanil pharmacokinetics in obese versus lean patients. ANESTHESIOLOGY 1998; 89:562-73