Prospective Use of Population Pharmacokinetics/ Pharmacodynamics in the Development of Cisatracurium[1]

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Purpose. The population PK/PD approach was prospectively used to determine the PK/PD of cisatracurium in various subgroups of healthy surgical patients.

Methods. Plasma concentration (Cp) and neuromuscular block data from 241 patients in 8 prospectively-designed Phase I–III trials were pooled and analyzed using NONMEM. The analyses included limited Cp-time data randomly collected from 186 patients in efficacy/safety studies and full Cp-time data from 55 patients in pharmacokinetic studies. The effects of covariates on the PK/PD parameters of cisatracurium were evaluated. The time course of neuromuscular block was predicted for various patient subgroups.

Results. The population PK/PD model for cisatracurium revealed that anesthesia type, gender, age, creatinine clearance, and presence of obesity were associated with statistically significant ($p < 0.01$) effects on the PK/PD parameters of cisatracurium. These covariates were not associated with any clinically significant changes in the predicted recovery profile of cisatracurium. Slight differences in onset were predicted in patients with renal impairment and patients receiving inhalation anesthesia. Based on the validation procedure, the model appears to be accurate and precise.

Conclusions. The prospective incorporation of a population PK/PD strategy into the clinical development of cisatracurium generated information which influenced product labeling and reduced the number of studies needed during development.

KEY WORDS: pharmacokinetics; pharmacodynamic modeling; NONMEM; model validation; cisatracurium.

INTRODUCTION

The population pharmacokinetic/pharmacodynamic (PK/PD) approach was applied to the development of a new neuromuscular blocking agent, cisatracurium besylate (51W89 besylate, NIMBEX[5]), by incorporating the collection of sparse samples from patients in international efficacy/safety trials. The objectives were: to determine the PK/PD of the drug in healthy patients; to identify factors (e.g., obesity, gender) affecting the PK/PD of cisatracurium; to validate the model, thereby ensuring confidence in predictions from the model; to gain information for product labeling; and to decrease the number of formal pharmacokinetic studies needed during clinical drug development.

MATERIALS AND METHODS

Plasma cisatracurium concentrations (Cp) and neuromuscular block (NMB) data were collected from 109 patients in six pharmacokinetic studies and 258 patients in four efficacy/safety studies. All patients received an initial cisatracurium dose of 0.015 to 0.8 mg/kg administered intravenously. Some patients also received either multiple 0.03 mg/kg maintenance doses or an infusion of cisatracurium.

Blood Sampling

Each patient from PK studies had 17 samples (full sampling) collected from an intraarterial or intravenous catheter. Each patient from efficacy/safety studies had five venous samples (sparse sampling) collected according to a prospectively-designed randomization schedule. Three additional samples were collected from patients receiving infusions of cisatracurium for ≥30 minutes. One milliliter of plasma from each sample was stabilized with acid within 3 minutes of collection and frozen until analysis.[6]

NMB Data

NMB data were continuously measured using mechanomyography or electromyography (1) for 356 and 11 patients, respectively. NMB data measured at the time of each blood sample collection, and data describing the onset, depth, and duration of NMB were included in the analyses and were expressed as %block (relative to a baseline control).

Subsets of Data

Within each blood sampling profile type, data from 70% of the patients were randomly selected for inclusion in a model-development dataset (the dataset used in the determination of all PK/PD parameter estimates). Data from the remaining patients were included in a model-validation dataset (the dataset used to test the predictive ability of the multivariate PK/PD model).

All data analyses were performed using NONMEM, Version IV(2). Statistical differences ($p < 0.01$) between hierarchical models (with and without covariates) were determined by assessing the change in the objective function. For the validation dataset, predictions of Cp and %block were made within NONMEM; all other analyses were performed using SAS, Version 6.07.

Covariates

Study exclusion criteria were relaxed (i.e., there were no restrictions on weight, age, or screening laboratory values) in

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[5] Trademark of the Glaxo Wellcome group of companies registered in the US patent and trademark office.

[6] A validated HPLC method was used for determination of Cp. The lower limit of quantification was 10 ng/ml. Accuracy and precision were within $<\pm 8.6\%$ and $<13.4\%$. Personal communication: CD James, Glaxo Wellcome Inc.; August, 1995.

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most studies to allow for heterogeneity in the patient populations. The following covariates were prospectively identified for evaluation: gender, age, race, anesthesia type, estimated creatinine clearance (CrCl, 3), and the presence of obesity (actual body weight >30% over ideal body weight, 3). These covariates were chosen to account for potential physiologic changes which may affect the PK/PD of drugs in general and to ensure adequate evaluation of subgroups for product labeling. Site of sampling (arterial or venous blood) and complexity of sampling (full vs. sparse sampling) were also included in the modeling process (as controlling variables) to control for differences in study design (but not to test for arterio-venous differences in the PK/PD of cisatracurium). The effects of covariates and controlling variables were modeled using dichotomous parameterizations as outlined in Table I.

Pharmacostatistical Model

Because cisatracurium undergoes Hofmann elimination (a chemical process dependent on pH and temperature), the PK/PD of cisatracurium were described using a two-compartment open model with elimination from both compartments (4) and a hypothetical effect compartment. Because the rate of elimination from the peripheral compartment (k_{20}) couldn't be independently estimated, k_{20} was fixed at 0.0237 min^{-1}, the average rate constant describing the *in vitro* degradation of cisatracurium in plasma from a previous study in nine healthy volunteers (5).

Model Development

Univariate analyses were completed to determine the effect of each covariate on the CL, Vc, k_{eo}, and EC_{50}. The PK model was developed separately from the PD model to decrease runtimes. Multivariable analyses were completed using backward elimination to further determine the effect of each covariate on CL, Vc, k_{eo}, and EC_{50}. Finally, all PK/PD parameters and any statistically significant covariates were combined into a final multivariate PK/PD model and re-estimated.

Validation of Multivariate PK/PD Model

The final multivariate PK/PD model (including covariate effects) was then applied to the model-validation dataset. The differences between measured and predicted values for both the Cp and %block measurements were evaluated for accuracy and precision. The mean prediction error percent (MPP%; measure of bias) and the mean absolute prediction error percent (MAP%; measure of precision) were calculated for Cp and %block measurements (6).

Table I. Demographic Characteristics of 241 Healthy Adult Patients Included in Analyses

	Model-Development Dataset			Model-Validation Dataset		
		Number of Observations			Number of Observations	
Characteristic	Number of Patients (%)[a]	Concentrations	NMB	Number of Patients (%)[a]	Concentrations	NMB
Gender						
Male	97 (57.4)	723	1576	42 (58.3)	304	673
Female	72 (42.6)	406	1125	30 (41.7)	174	492
Age						
<65 years	137 (81.1)	919	2298	54 (75.0)	348	913
≥65 years	32 (18.9)	210	403	18 (25.0)	130	252
Estimated Creatinine Clearance						
≤70 mL/min	42 (24.9)	256	600	21 (29.2)	157	346
>70 mL/min	127 (75.1)	873	2101	51 (70.8)	321	819
Race[b]						
White	155 (91.7)	1034	2460	66 (91.7)	429	1053
Black	11 (6.5)	75	197	1 (1.4)	4	12
Other	3 (1.8)	20	44	5 (6.9)	45	100
Presence of Obesity[c]						
Non-obese	135 (79.9)	958	2141	56 (77.8)	402	899
Obese	34 (20.1)	171	560	16 (22.2)	76	266
Site of Sampling						
Venous	146 (86.4)	819	2283	60 (83.3)	313	932
Arterial	23 (13.6)	310	418	12 (16.7)	165	233
Anesthesia Type						
Inhalation	87 (51.5)	586	1269	40 (55.6)	281	616
Opioid	82 (48.5)	543	1432	32 (44.4)	197	549
Complexity of Sampling						
Full Sampling	38 (22.5)	518	694	17 (23.6)	229	322
Sparse Sampling	131 (77.5)	611	2007	55 (76.4)	249	843

[a] Percent of patients in the model-development and model-validation dataset, respectively.
[b] Evaluations of race were made by comparing the black population with the white and other populations combined.
[c] Actual body weight > 30% over ideal body weight.

RESULTS

A total of 1607 Cp and 3866 %block observations from 241 patients were included in the analysis (Figure 1)[7]. Demographics are summarized in Table I. There were wide ranges of age, weight, percent ideal body weight, and CrCl in the dataset. The demographic characteristics were similar in the model-development and model-validation datasets. The age ranged from 19 to 86 years and CrCl ranged from 28 to 197 ml/min.

Multivariate PK/PD Model[8]

Table II summarizes parameter estimates for the base population from the final multivariate PK/PD model. *The base population represents 19–64 year-old, nonobese, male patients with CrCl > 70 ml/min who received cisatracurium during opioid anesthesia and had full (venous) sampling.* The % increase or decrease ($p < 0.01$) in CL, Vc, k_{eo} and EC_{50} associated with each covariate is summarized in Table III. The magnitude of all the covariate effects was relatively small except for the effect of anesthesia type on Vc and k_{eo}.

The clinical significance of these findings was determined by examining predicted Cp and %block vs. time profiles following a 0.1 mg/kg bolus dose of cisatracurium in a hypothetical patient from the base population and in a hypothetical patient with each covariate producing effects on CL, Vc, k_{eo} or EC_{50}. When evaluating the %block-time profiles, the following times were specifically noted: the time to 90% block (a measure of drug onset), time to 25% recovery, and time to 75% recovery (measures of drug offset).

Predicted Cp vs. time data following a single 0.1 mg/kg bolus dose of cisatracurium were similar for the patient from the base population and for patients with each covariate affecting the CL or Vc with two minor exceptions. For a patient receiving inhalation anesthesia, the predicted Cp was initially slightly lower than for a patient receiving opioid anesthesia (i.e., the base population); however, by 20 to 30 minutes, this trend was reversed. For an obese patient, the predicted Cp was similar to a patient from the base population between 0 and 20 minutes, but became slightly higher after 20 to 30 minutes for the obese patient.

A plot of the predicted %block vs. time data following a single 0.1 mg/kg bolus dose of cisatracurium is presented in Fig. 2 for each patient covariate producing effects on PK/PD parameters of cisatracurium. The model predicts that the average times to 90% block were within ±30 seconds of values predicted for the patient in the base population, the female patient, the obese patient, and the elderly patient. However, the model predicts that the average times to 90% block were 44 seconds faster for the patient receiving inhalation anesthesia than for a patient receiving opioid anesthesia and 39 seconds slower for the patient with a CrCl of 28 to 70 ml/min than for the patient with a CrCl > 70 ml/min. The average times to 25% recovery and 75% recovery for all patient subgroups were within ±3 minutes and ±4 minutes, respectively, of the base population.

[7] Plasma samples from 54 patients with full sampling and 72 patients with sparse sampling were lost due to bioanalytical problems. All data presented henceforth represents those 241 patients with available Cp data.

[8] Further information regarding these analyses is available upon request.

Validation of Model

The precision and bias for the Cp and %block measurements are summarized for the whole population and each subgroup (Table IV).

The difference between the predicted Cp and the corresponding measured Cp (MPP%) averaged <10% of the predicted Cp in all subgroups. The absolute difference between the predicted and observed Cp (MAP%) averaged <25% of the predicted Cp.

Predictions of the pharmacodynamic observations showed marked bias and less precision than the pharmacokinetic observations (Table IV). However, 17 of 1165 NMB observations appeared to be outliers (individual MAP% and MPP% values were >±200). Most of these outliers occurred close to 95% recovery and may be related to differences between baseline and end-control responses, limitations in the determination of pharmacokinetic parameters (assumptions regarding k_{20}), and/or limitations in the determination of k_{eo}.

The precision and bias improved substantially when data from these outliers were excluded (Table IV). The MAP% for %block observations, excluding the outliers, was less than 17% of the predicted %block for all subgroups. The MPP% for %block observations, excluding outliers, was between −15% and −1% of the predicted %block for all patient subgroups, indicating that, on average, the predicted %block was slightly higher than the measured %block.

DISCUSSION

This report describes a prospectively-designed example of the population PK/PD approach used during the clinical development of a new drug. The population PK/PD model (controlling for complexity of blood sampling and site of sampling) revealed that anesthesia type, gender, age, CrCl, and the presence of obesity were associated with statistically significant effects on CL, Vc, k_{eo} or EC_{50} for cisatracurium. These covariates were not associated with any clinically significant changes in the predicted recovery profile of cisatracurium. Slight differences in onset were predicted in patients with renal impairment and in patients receiving inhalation anesthesia. Based on the validation procedure, the model appears to be accurate and precise.

Results from these analyses were used to improve dosing guidelines in product labeling and to decrease the number of studies needed in the drug development process, as discussed below.

Improvement in Dosing Guidelines

The present analyses supported the recommendation that dosage adjustments are not necessary in many specific patient populations. First, the low magnitude of interpatient variability in CL (16%) verified that, as expected, tight physiologic control of pH and temperature results in little variability in Hofmann elimination between patients. This quantification of variability has been incorporated into product labeling (7). Second, because of the low interpatient variability in the pharmacokinetics of cisatracurium, there appeared to be adequate power to detect even small (<15%) highly statistically significant effects of covariates on the PK/PD parameters of cisatracurium. These effects were not associated with any clinically significant

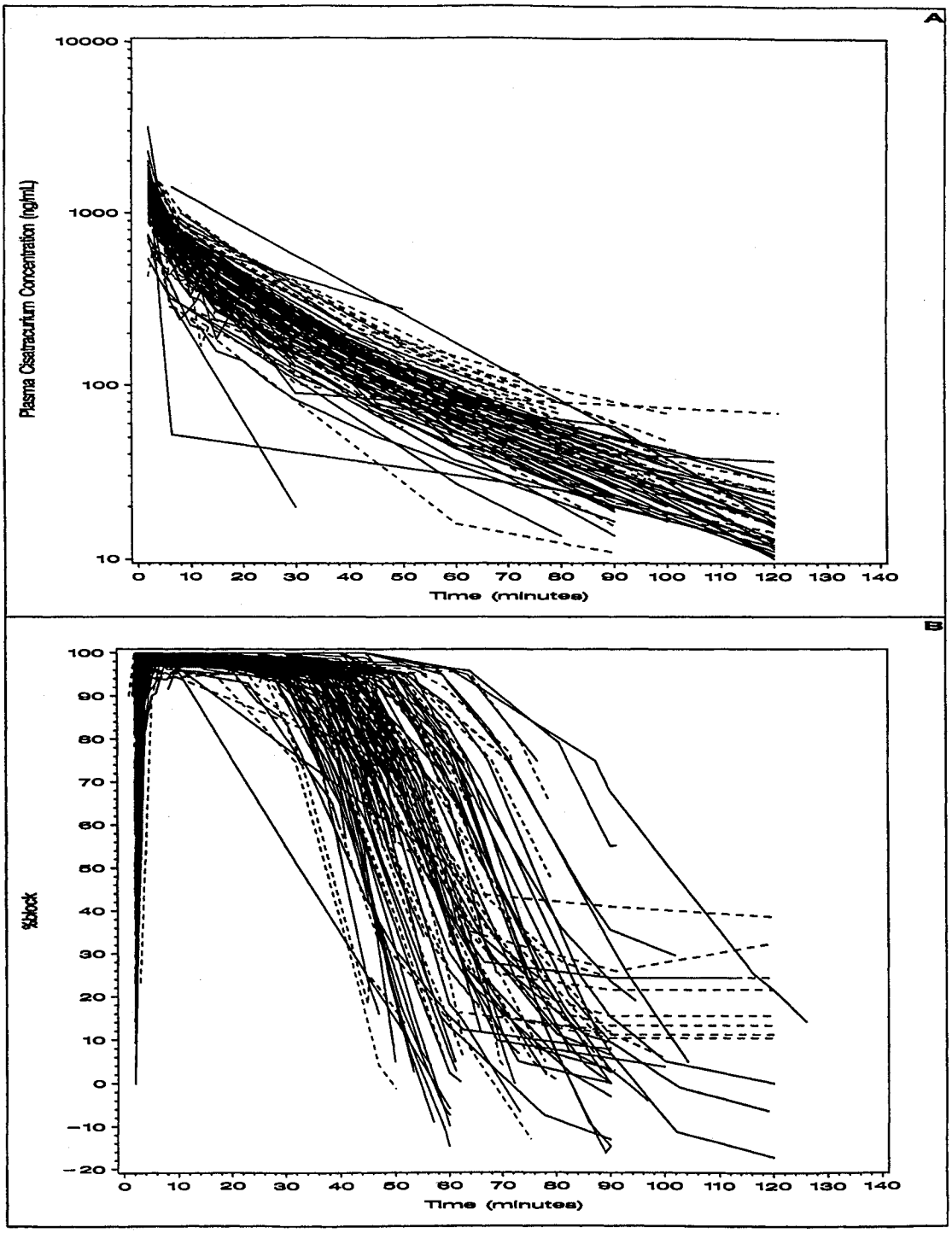

Fig. 1. Plasma cisatracurium concentration-time data (A) and %block-time data (B) are illustrated for patients receiving 0.1 mg/kg cisatracurium. Patients from the model-development dataset are illustrated using solid lines, while patients from the model-validation dataset are illustrated using the dashed lines.

changes in the predicted recovery profile of cisatracurium. Therefore, special dosage recommendations are not necessary for the populations studied (e.g., renal dysfunction, inhalation anesthesia, gender, obesity, and race). However, because slight differences in onset were predicted in patients with renal impairment and in patients receiving inhalation anesthesia, these patients may require adjustments in the timing of intubation. An explanation of these effects is provided below.

Renal Dysfunction

While there were no differences in the pharmacokinetics of cisatracurium in patients with mild to moderate renal dys-

Table II. PK/PD Parameter Estimates of Cisatracurium in Patients from the Base Population[a]

Parameter	Estimate (% SEM)[b]	Magnitude of Interpatient Variability[c] CV (% SEM)
CL (mL/min/kg)	4.57 (2.8)	16.3% (19.9)
V_c (mL/kg)[d]	45.7 (9.1)	27.3% (33.1)
V_p (mL/kg)[d]	98.8 (7.0)	
Q (mL/min/kg)	5.69 (4.4)	
k_{eo} (min^{-1})	0.0575 (11.6)	60.9% (30.7)
EC_{50} (ng/mL)	141.0 (5.9)	51.7% (35.4)
S (unitless)	4.01 (3.6)	
Residual Variability[c]—Cp expressed as a CV (% SEM)	25.3% (15.2)	
Residual Variability—%block expressed as a SD[e] (% SEM)	7.1 (9.8)	

[a] The base population represents 19 to 64 year old, nonobese male patients with CrCl values greater than 70 mL/min who received cisatracurium during opioid anesthesia and had full (venous) sampling.
[b] Presented as the estimate with the percent standard error of the mean (% SEM; a measure of precision) indicated within parentheses.
[c] Modeled using a proportional error model; expressed as a coefficient of variation with % SEM indicated within parentheses.
[d] V_{ss} is equal to the sum of V_c and V_p.
[e] Modeled using an additive error model; expressed as a standard deviation with % SEM indicated within parentheses.

Table III. Summary of the Changes in the CL, Vc, k_{eo} and EC_{50} of Cisatracurium Associated with Statistically Significant Patient Covariates

Parameter	Patient Covariate	% Increase (↑) or Decrease (↓) in Parameter (% SEM)[a]
CL	Presence of Obesity	12% ↓ (33.6)
Vc	Elderly	15% ↑ (41.2)
	Inhalation Anesthesia	65% ↑ (32.0)
k_{eo}	Inhalation Anesthesia	78% ↑ (28.8)
	Creatinine Clearance ≤70 mL/min	16% ↓ (40.8)
	Presence of Obesity	16% ↑ (56.0)
	Female	14% ↑ (46.8)
EC_{50}	Inhalation Anesthesia	15% ↓ (30.1)
	Elderly	5% ↓ (154.1)
	Controlling Variables:	
CL	Collection of Arterial Blood	4% ↑ (174.1)
k_{eo}	Collection of Arterial Blood	18% ↓ (71.5)
	Sparse Sampling	13% ↓ (67.6)

[a] Presented as the estimate of the patient covariate effect, with the associated percent standard error of the mean (% SEM; a measure of precision) indicated within parentheses.

function, the k_{eo} was 16% smaller. This difference was associated with a slightly (~40 sec) slower predicted time to onset following a 0.1 mg/kg bolus dose of cisatracurium. However, there were no clinically significant differences in the predicted recovery profile of cisatracurium for this subgroup. These results suggest that dosage requirements are not changed in patients with renal dysfunction. However, due to the slower onset of action, product labeling recommends extending the interval between administration of cisatracurium and the intubation attempt to achieve adequate intubation conditions in these patients (7).

Anesthesia Type

The use of inhalation anesthesia was associated with a 65% larger Vc (a 21% larger Vss)[9], a 78% larger k_{eo}, and a 15% lower EC_{50} for cisatracurium. These changes resulted in a slightly faster (~45 sec) predicted time to onset in patients receiving 0.1 mg/kg cisatracurium during inhalation anesthesia than in patients receiving opioid anesthesia; however, there were no clinically significant differences in the predicted recovery profile of cisatracurium for this subgroup. This interaction is physiologically based [i.e., increase in volume is most likely due to changes in regional blood flow (e.g., to skin and muscles) associated with the use of inhalation anesthesia (9)], but may not affect dosage recommendations. Because patients in the present study received cisatracurium during stable anesthesia while patients in the clinical setting receive cisatracurium closer to induction of anesthesia, the faster onset predicted by the present model may/may not be clinically significant in general clinical practice. Although this finding did not affect dosage recommendations, it is useful information for the design of future studies (i.e., anesthesia type should be standardized in studies of intubation conditions and timing).

Gender, Obesity, Age, and Race

Gender and the presence of obesity produced small changes in CL and/or k_{eo}. These effects were not associated with any clinically significant alterations in the predicted onset or recovery profile for cisatracurium, and therefore, warranted no changes in dosage recommendations (7).

Because the effect of advanced age on EC_{50} was estimated with poor precision in the present analyses, results from other investigators (10) are probably more representative of the effects of advancing age on the PK/PD profile of cisatracurium. The evaluation of race was limited by the small number of patients who were nonwhite, but one would predict that the pharmacokinetics of cisatracurium would not be dependent on race since its elimination is dependent on pH and temperature.

Lastly, the present population PK/PD model allowed for a better understanding of the variability in the time course of effects, which was summarized in product labeling (7). Specifically, the magnitudes of interpatient variability in k_{eo} and EC_{50} (~50–61%) were much higher than those observed for CL and Vc (~16–27%), indicating that alterations in the time course

[9] Vc and Vp should not be interpreted physiologically (8); Vss, the apparent volume of distribution at steady state, (the sum of Vc and Vp) should be used as the basis of physiologic interpretation.

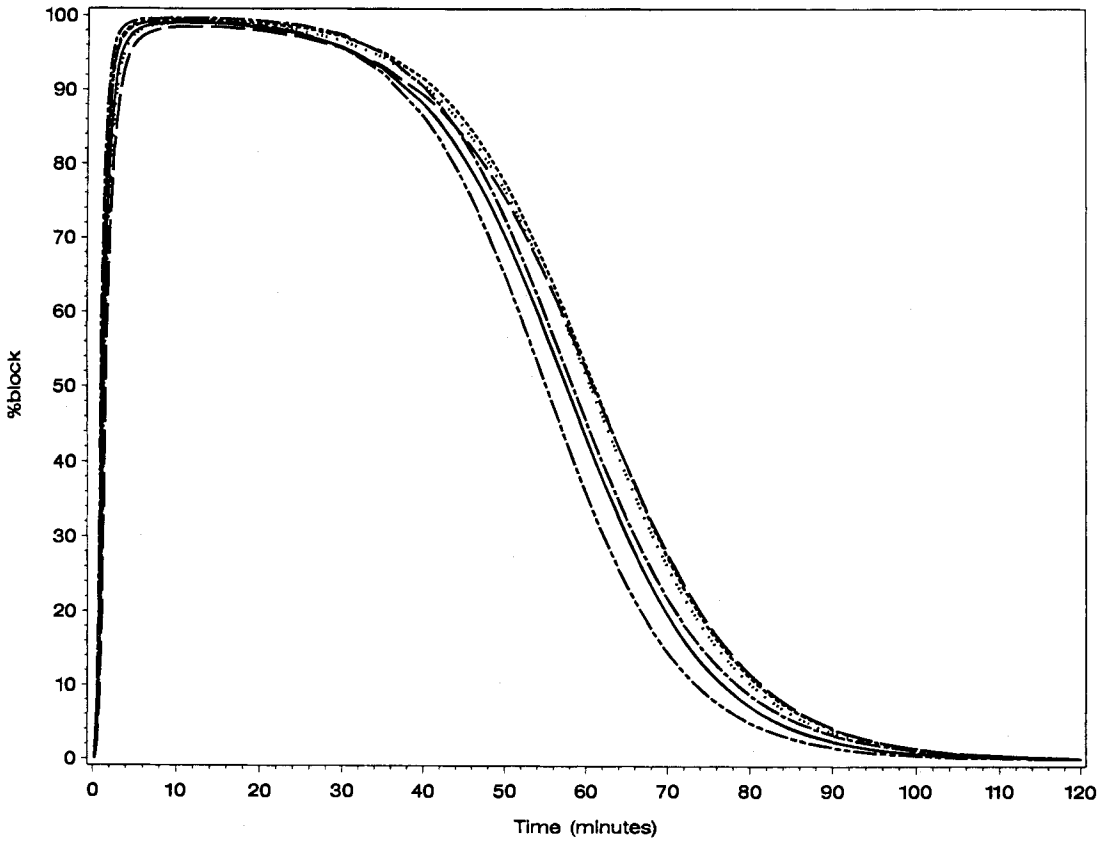

Fig. 2. A plot of the predicted %block vs. time data following a single 0.1 mg/kg bolus dose of cisatracurium for a hypothetical patient from the base population (solid line). The base population is represented by a 19 to 64 year old, nonobese, male adult patient with a CrCl value >70 ml/min who received cisatracurium during opioid anesthesia and had full (venous) sampling. Predicted %block vs. time data are as presented for the following hypothetical patients: a patient receiving inhalation anesthesia (--), an obese patient (-------), an elderly patient (··· · ···), a female patient (__—__), and for a patient with a CrCl between 28 and 70 ml/min (— —).

Table IV. Measures of Precision and Bias for Plasma Cisatracurium Concentrations and NMB

	Plasma Cisatracurium Concentrations (n = 478)			NMB					
				All Observations (n = 1165)			Observations Minus Outliers (n = 1148)[a]		
Patient Subgroup	n	MAP%[b]	MPP%[c]	n	MAP%[b]	MPP%[c]	n	MAP%[b]	MPP%[c]
Base population	51	22.7	−4.7	72	16.3	−14.7	72	16.3	−14.7
Elderly	130	23.2	−9.2	252	83.0	29.8	244	15.8	−7.5
Inhalation Anesthesia	281	23.5	−3.4	616	67.1	36.5	602	14.6	−3.8
CrCL ≤ 70 mL/min	157	21.0	−7.4	346	64.6	25.9	335	11.9	−4.9
Presence of Obesity	72	14.6	−0.6	258	14.6	−0.3	255	9.8	−5.3
Female	174	22.8	−4.3	492	15.1	0.8	489	12.5	−1.9
Overall population	478	23.0	−3.2	1165	43.1	17.0	1148	14.5	−4.7
Collection of Arterial Blood	165	22.0	−9.8	233	155.3	104.2	219	16.8	−2.3
Sparse Sampling	249	23.3	2.9	843	14.9	−3.7	840	13.7	−4.2

[a] Seventeen pharmacodynamic observations were excluded from this analysis.
[b] MAP% is the mean absolute prediction error percent, a measure of precision.
[c] MPP% is the mean prediction error percent, a measure of bias.

of cisatracurium-induced block are more likely due to variability in the pharmacodynamic parameters than in the pharmacokinetic parameters.

Number of Studies

By prospectively incorporating the use of a population PK/PD approach, relaxing inclusion/exclusion criteria, and studying the drug under various dosing regimens in efficacy/safety studies, sufficient heterogeneity of data can be obtained to predict the time course of drug effects in patient subgroups following a variety of dosage regimens. Using a traditional approach, this information would be obtained from formal PK/PD studies (treating separate groups of patients) with a fixed dosing regimens; thereby, increasing the total number of studies and patients needed to adequately describe the PK/PD of the drug. Furthermore, if the traditional approach is not coupled with PK/PD modeling, the information gained from formal studies is only relevant to the studied dosing regimen. By considering these theoretical concepts when designing the population PK/PD program for cisatracurium, four formal PK/PD studies were rendered unnecessary. These studies included evaluations of obesity, mild to moderate renal dysfunction, drug interaction with inhalation agents, and dose proportionality (data not shown).

Validation of the Multivariate PK/PD Model

The validation procedure demonstrated that the PK/PD model predicted Cp and NMB observations with acceptable accuracy and precision for the group as a whole and for patient subgroups. Therefore, the prospective plan for validation of the PK/PD model allowed for more confidence in the predictions from the model.

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