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Mixed Effect Modeling of Sumatriptan Pharmacokinetics During Drug Development: II. From Healthy Subjects to Phase 2 Dose Ranging in Patients

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Sumatriptan is indicated for the treatment of migraine attack and cluster headache; it is currently marketed as a subcutaneous injection, nasal spray, and oral tablet. New formulations are under consideration. The knowledge of sumatriptan absorption, combined with PK/PD information would help the design of more efficient formulations. In this perspective, we attempted to model the absorption of sumatriptan by population PK analysis. Data following administration by the intravenous (iv), the subcutaneous (sc), and the oral (po) route in healthy subjects were analyzed. A large database with full kinetic profiles was constituted. Sumatriptan was administered to 215 healthy subjects (iv, sc, and po) and to 143 migraine sufferers (po). The mean age was 31 years (18–86 years) in healthy subject population and was 38 years (18–65 years) in migraine patients. The mean weights were 74 kg (54–104 kg) and 66 kg (38–136 kg) in healthy subjects and migraine patients, respectively, and the mean heights were 176 cm (157–193 cm) and 164 cm (152–183 cm) in healthy subjects and migraine patients, respectively. A NONMEM analysis was performed using a two-compartment disposition model. Oral absorption was modeled with a first-order input followed by a zero-order input. Less biased results were obtained using the FOCE method. The total clearance and the distribution volume at steady state were 71.2 L/hr and 94.5 L after iv dosing and 68.7 L/hr and 109 L after inclusion of the sc and po data. The absorption phase appeared to last for about 5 hr. The interindividual variability of the main PK parameters was low: It was around 20% for the total clearance and around 30% for the distribution volume at steady state. Although significant, the combination of age and height on clearance did not decrease considerably the interindividual variability of this parameter (decrease of 2.2%); nor was it possible to establish clearly if a migraine attack has an effect on drug absorption because of the sampling scheme during absorption. Simulations have shown that it would have been possible to estimate all the PK parameters with a data set reduced to one quarter of its actual number of samples.

KEY WORDS: sumatriptan pharmacokinetics; population analysis; NONMEM; migraine; data reduction.

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INTRODUCTION

Sumatriptan is currently marketed as a subcutaneous injection, nasal spray, and oral tablet for the acute treatment of migraine attack and as a subcutaneous injection for treatment of cluster headache. Sumatriptan is rapidly absorbed after both subcutaneous and oral dosing. The mean absolute bioavailability is 96% for the subcutaneous route and 14% for the oral route. The pharmacokinetics of sumatriptan are similar in healthy young subjects, healthy elderly subjects, and in migraine patients and are linear over the subcutaneous dose range 1–16 mg and the oral dose range 25–400 mg. Sumatriptan has a mean apparent volume of distribution of 170 L and the mean total plasma clearance is approximately 70 L/hr with the renal clearance representing 20% of the total. Sumatriptan is eliminated primarily (80%) by metabolism, mediated by the monoamine oxidase A isoenzyme (1). Metabolism is responsible for the low oral bioavailability with gut and hepatic first-pass effect. Oral sumatriptan displays a particular absorption profile with a large peak or two main peaks. To describe processes that occur during absorption, a deconvolution analysis was performed (2). Data from healthy subjects and from migraine patients during a pain-free period and a migraine attack were available. This analysis which combines Phase 1 and Phase 2 data was performed retrospectively to identify which development steps could have benefited from population approach in terms of cost and time savings. More specifically, the objectives of this population modeling work were (i) to perform prospective simulations and improve the design of PK studies, and (ii) to study the absorption and help in designing new formulations.

MATERIALS AND METHOD

Healthy Subject Data

Healthy subject data came from clinical pharmacology studies: six bioavailability/bioequivalence studies and three tolerability studies. Data consisted of full kinetic profiles, up to 12 or 24 hr postdose, following administration by the intravenous (2- and 3 mg doses), the subcutaneous (1-, 2-, 3-, 4-, 6-, 8-, 12-, and 16-mg doses), and the oral route (25-, 50-, and 100-mg conventional tablets). The data of 215 healthy subjects were recorded in the data set with only seven females.

Migraine Patient Data

Three dose levels of sumatriptan were studied in a double-blind, placebo-controlled, parallel efficacy study. The migraine patients were

Table I. Demographic Covariates of Healthy Subject Population, Intravenous Route, and All Routes, and Patients' Population, Oral Route

Covariates	Healthy subjects		Patients oral route
	Intravenous route	All routes	
No. of subjects	23	215	143
No. of observations	418	4091	833 (pain-free period) 794 (migraine attack)
Age (years)	28	31	38
Range	19–41	18–86	18–65
Weight (kg)	72	74	66
Range	58–88	54–104	38–136
Height (cm)	176	176	164
Range	167–185	157–193	152–183
Gender			
men	23	208	9
women	0	7	134

treated on the two following occasions: during a migraine attack and during a pain-free period.

During the migraine attack 43 patients received 25 mg, 47 patients received 50 mg, and 49 subjects received 100 mg. During the pain-free period 46 patients received 25 mg, 44 patients received 50 mg, and 47 patients received 100 mg. Blood samples were collected at 0.25, 0.5, 1, 1.5, 2, 3, and 4 hr postdose. The data of 143 patients were recorded in the data set with only nine males.

Database

To study the intravenous route by itself, a data set was built, constituted of 418 time–concentration points collected in 23 healthy male subjects. When all the routes were pooled together, we obtained a population of 215 healthy subjects with 4091 time–concentration points (23 intravenous kinetic profiles, 125 subcutaneous kinetic profiles, and 115 oral kinetic profiles).

To study the migraine effect, the healthy subject data were pooled first with the migraine patient data during a pain-free period and second with the data from the same migraine patients during a migraine attack. Three hundred fifty-two subjects constituted the first population (215 healthy subjects and 137 migraine patients during a pain-free period) with 4924 observations, 354 subjects constituted the second population (215 healthy subjects and 139 migraine patients during a migraine attack) with 4885 observations.

Table I presents the demographic distribution of the healthy subject and migraine patient populations.

Analytical Method

The plasma samples were analyzed using a validated high-performance liquid chromatographic (HPLC) method with electrochemical detection. The lower limit of quantification for the HPLC method was 1 ng/ml (3).

Data Analysis

NONMEM, version IV running on a Vax machine (DEC) was used to perform the analysis (4).

Base Model

An open *two-compartment disposition model* parameterized in clearances and volumes was fitted to the intravenous data. The interindividual variability was modeled with an exponential error model. Both the first-order estimation (FO) and first-order conditional (FOCE, with interaction) methods were used (4).

Different intraindividual error models were tried to improve the quality of fit (i) An additive error model; (ii) a proportional error model; and (iii) a combination error model expressed as: $W = \sqrt{1 + \theta^2 \cdot F^2}$, $Y = F + W \times ERR(1)$; where θ is the ratio of the proportional component variance to the additive component (Sheiner, NONMEM User Net Contribution 12/12/94).

The overall goodness of fit of the structural model was evaluated by graphical analysis of predicted concentrations vs. observed concentrations (distribution of the points on the unit line) and weighted residuals vs. predicted concentrations (distribution of the points on the zero line). The precision of the parameter estimate was given by the standard error of the estimate: We considered that a parameter was correctly estimated when the ratio of standard error to the parameter estimates (CV) was less than 0.5.

To build a common compartmental model for intravenous, subcutaneous, and oral data, deconvolution was performed on individual subjects' data (Study B) using PCDCON package, version 1.0 (5,6) to assess the *absorption profile for the oral route.*

Covariate Effects

The continuous covariates available were the weight in kilograms, the height in centimeters, and the age in years. The dichotomous covariates available were the gender and a flag coding for "being a migraineur."

The statistical procedure for the selection of the covariates used that described by Maitre *et al.* (7) and improved by Mandema *et al.* (8). Potential linear or nonlinear relationships between the individual Bayesian estimates and covariates were investigated using a generalized additive model (GAM).

Plots of partial residuals were used to describe the relationships with covariates. All calculations used S-PLUS package version 3.2 release 1 (9). Last, a final model with relevant covariates was built from the base model obtained using FO method. The covariates were selected in NONMEM model at $p = 0.005$, with a difference in −2 log-likelihood (−2LL) equal or greater than 7.8 (−2LL is asymptotically distributed as chi-square and the degree of freedom equal to the number of new parameters).

Simulations

To mimic different scenarios or study design, reduced data sets were obtained from total data set by two different methods:

- Random selection of concentration/time points, using SAS for Windows (version 6.08): up to 4.3 concentration–time pairs per subject.
- Optimal design, using APIS (version 3.05a), based on the principle of D-optimality (11). Four samples (iv and sc dosing) and five samples (po) were selected, based on human PK parameters predicted by allometric interspecies scaling (10): 77 L/hr for total clearance, 19 L for central volume, 214 L/hr for intercompartmental clearance, and 137 L for distribution volume at steady state.

RESULTS

Sumatriptan Pharmacokinetic After Intravenous Administration

Base Model

Using FO method, the disposition of sumatriptan is better described by a model with additive error than by models with proportional or combination error. With proportional error or combined error model, at low concentrations (less than 5 ng/ml), most of the concentrations were underpredicted. The estimates of the total clearance were 90 L/hr and 113 L/hr, and the estimates of the distribution volume at steady state were 146 L and 113 L using proportional and combined error model, respectively. The standard error of estimates on total clearance intersubject variability was also high: >100% for the intraindividual proportional error model, 85% for the combination error model. With the additive error model, the distribution phase is rapid ($t_{1/2}\alpha$ around 4 min), the total clearance is 80 L/hr, the distribution volume at steady state is 80 L and the elimination half-life is 1.17 hr. The interindividual variability expressed as coefficient of variation is about 30% on clearances, 40% on central compartment volume, and the interindividual variability for distribution volume at steady state cannot be estimated (too low). All the parameters are correctly estimated (as defined previously).

The use of the FOCE method with interaction and a proportional error model improves the fit, as shown on the weighted residuals vs. predictions plot (Fig. 1): The points are better distributed around the zero line, and the scatterplot has a less "conical" shape. Distribution phase ($t_{1/2}\alpha$ of 5 min) is not different from previous results, the total clearance is 70 L/hr, the distribution volume at steady-state is 95 L and the elimination half-life is 1.6 hr. The intersubject variabilities are nearly half than those estimated with the FO method: The variance of total clearance is equal to 17% and the distribution volume at steady-state variance is equal to 14%.

The results obtained with different models tested and using different methods are presented in Table II.

Covariate Effects

Relationships between individual PK parameters obtained after the post-hoc estimation (i.e., total clearance and central compartment volume) and covariates (i.e., age, height, weight) were investigated using a GAM function with S-plus. Age significantly explains part of the clearance variability ($p = 0.015$), and weight part of the central compartment volume variability ($p = 0.015$). Although the partial residuals vs. covariates plots do not indicate clearly the type of relationship (Fig. 2), a linear relationship seems appropriate to include in the final NONMEM model.

Covariate effects were entered one by one in NONMEM in a linear model. Only height was found to affect the clearance ($p < 0.001$), and height and weight to affect the volume ($p < 0.005$, $p < 0.005$ respectively). Considering the high correlation existing between height and weight in this adult population, only the height, was retained

$$CL = \theta_1 + \theta_2 \cdot (HGT - 167), \qquad \theta_1 = 58.8, \qquad \theta_2 = 2.28$$

$$V = \theta_1 + \theta_2 \cdot (HGT - 167), \qquad \theta_1 = 11.4, \qquad \theta_2 = 0.662$$

The final results of the analysis of covariates are summarized in Table III.

The total clearance increases linearly with the height from the minimal value of 59 L/hr for the smaller subjects to 100 L/hr for the taller subjects. The central compartment volume increases linearly with the height from the minimal value of 11 L for the smaller subjects to 23 L for the taller subjects. When introducing height in the total clearance model, the interindividual variability on clearance decreases by 8.6%. When introducing height in the central compartment volume model, the interindividual variability on volume decreases by 6.9%. The plot of weighted residuals vs. predictions shows low concentration points better centered around zero (Fig. 3).

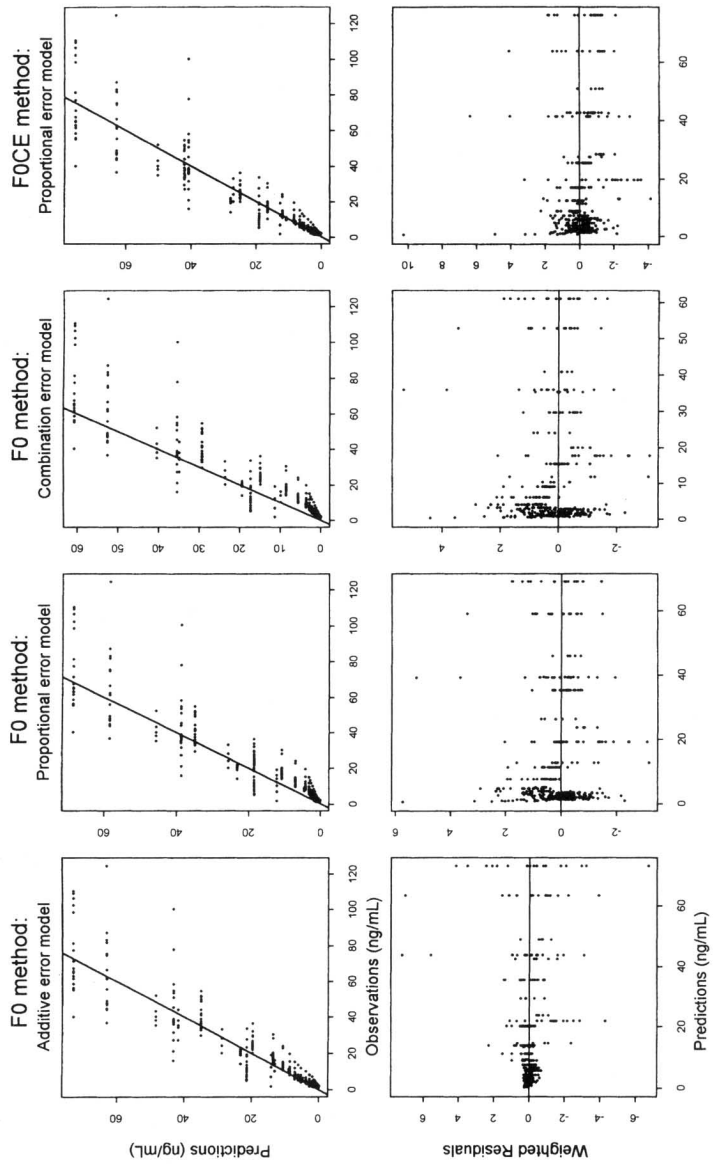

Fig. 1. Plots of predictions vs. observations and weighted residuals vs. predictions for intravenous data after modeling with different intraindividual error models or using different estimation methods. The FOCE method and proportional error model combine better distribution of the points around the unit line and less "conical" shape of the plot of weighted residuals vs. predictions.

Table II. Population Pharmacokinetic Parameter Estimates After Sumatriptan Intravenous Administration: Selection of the Structural Model[a]

Parameters	FO method			FOCE method
	$Y = F + err$	$Y = F \cdot (1 + err)$	$Y = F + err \cdot \sqrt{1 + \theta^2 \cdot F^2}$	$Y = F \cdot (1 + err)$
Disposition				
CL (L/hr)	80.2 (4.38)	89.2 (16.3)	113 (15.5)	71.2 (4.69)
V (L)	15.4 (7.14)	18.2 (10.4)	19.4 (9.02)	17.9 (7.82)
Q (L/hr)	80.7 (6.86)	67.8 (8.79)	68.1 (11.7)	69 (6.35)
V_{ss} (L)	78.9 (7.52)	146 (15.3)	123 (9.27)	94.5 (6.71)
Interindividual variability (CV%)				
ω_{CL}	31.5 (37.8)	39 (> 100)	69.9 (85.3)	17.3 (45.7)
ω_V	37.2 (28.9)	28.6 (28.8)	29.3 (18.5)	nc
ω_Q	29.4 (37.7)	33.5 (57.9)	56.9 (87.7)	nc
$\omega_{V_{ss}}$	—	80.8 (82.7)	47.2 (59.6)	13.9 (56.5)
Intraindividual error				
σ	25.2 (44.1)	74.5 (49.4)	0.0488 (49.4)	21.5 (11.1)
θ	—	—	1.14 (34.3)	
Derived parameters				
$T_{1/2}$ (hr)	1.17	2.36	1.74	1.61

[a]Numbers in parentheses are standard error of estimates in percentage.

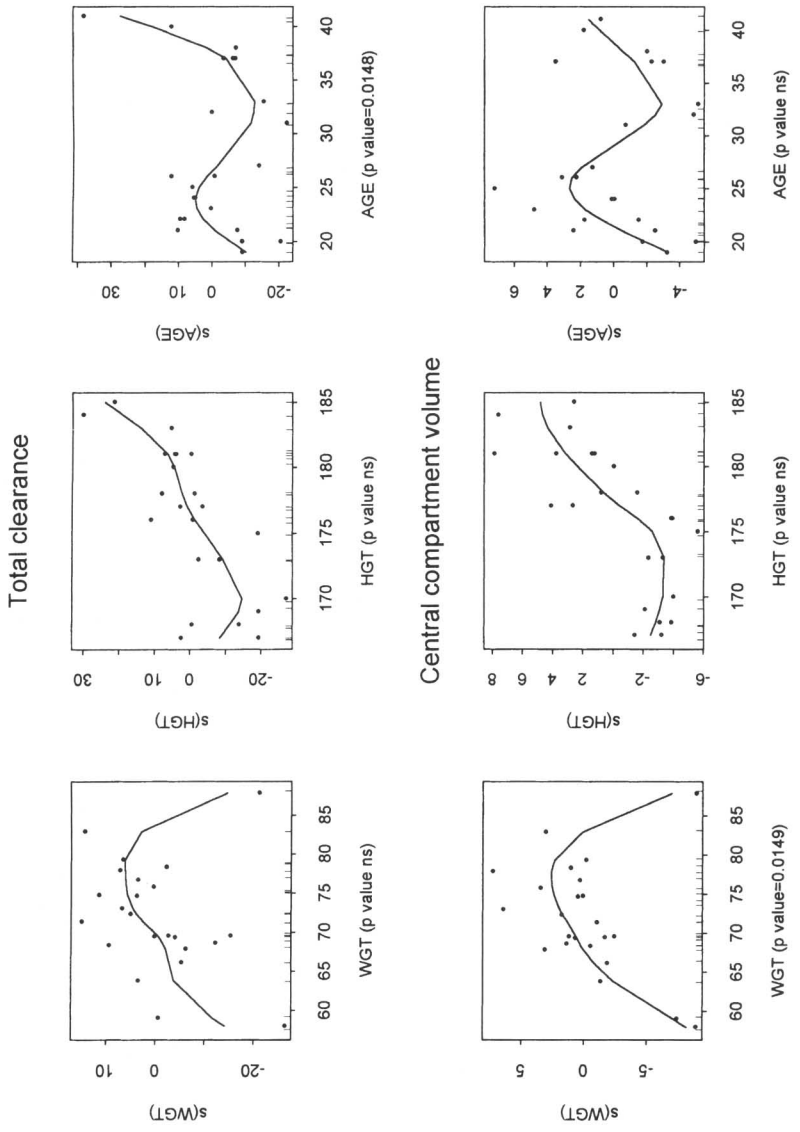

Fig. 2. GAM analysis for total clearance and central compartment volume of the intravenous data: Plots of the partial residuals vs. covariates. Each plot represents the contribution of a term to the additive predictor of the parameters.

Table III. Effect of Covariates on Pharmacokinetic Parameters After Intravenous Administration[a]

Parameters	Covariate effect model[b]	
	$CL = \theta_1 + \theta_2 \cdot (HGT - 167)$	$V = \theta_1 + \theta_2 \cdot (HGT - 167)$
Difference in −2LL	11	17
p-value	< 0.001	< 0.0005
Disposition		
CL (L/hr)		
θ_1	58.8 (12.6)	78.8 (4.8)
θ_2	2.28 (34.2)	
V (L)		
θ_1	15.6 (7.18)	11.4 (8.77)
θ_2		0.662 (22.4)
Q (L/hr)	82 (6.72)	78.4 (6.65)
V_{ss} (L)	76.3 (10)	80 (7.23)
Interindividual variability (CV%)		
ω_{CL}	22.9 (45.1)	31.1 (34.3)
ω_V	37 (29.4)	30.3 (28.2)
ω_Q	32.4 (31.5)	25.9 (47)
$\omega_{V_{ss}}$	—	—
Intrainindividual error		
σ	25.3 (43.9)	25.2 (44)

[a]Numbers in parentheses = SE of estimate (%).
[b]Model with additive intraindividual error using FO method.

Sumatriptan Pharmacokinetic After Oral Route (Total Data Set)

Base Model

Sumatriptan often displays either a large peak or two main peaks and, in both cases, the absorption lasts approximately 5 hr. Deconvolution analysis was performed on subjects with intravenous and oral data to determine the absorption profile. As shown in Fig. 4, the input rate profile presents two phases, which can be described by juxtaposition of a first-order and a zero-order absorption process. The parameters that characterize sumatriptan absorption are a lag time and a rate of absorption (ka) for the first-order process, a lag time and an infusion duration (D) for the zero-order process, and the ratio of the amount absorbed between the two processes. The combination of the two processes is very versatile and is able to fit either a double peak or a large peak, depending on their respective start time.

The addition of the absorption model allowed us to fit iv, sc, and po data simultaneously. The results of the selection of the structural model are presented in Table IV.

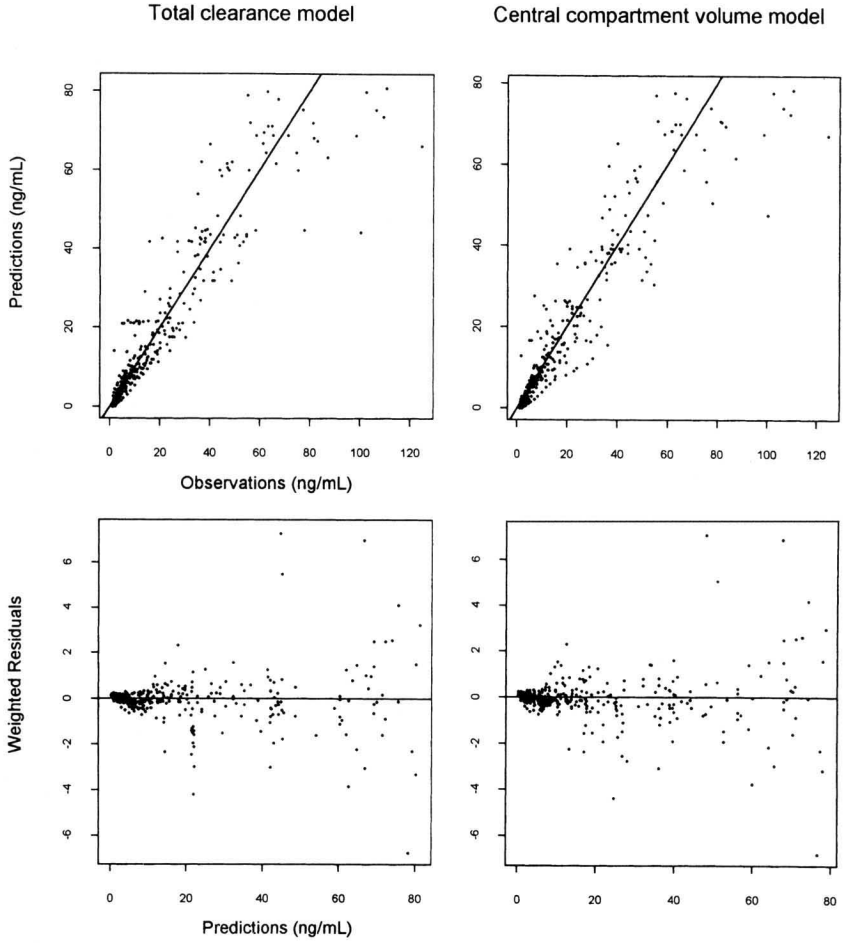

Fig. 3. Effect of the covariates on the parameter models for intravenous data after modeling with intraindividual additive model using FO method.

As illustrated by Fig. 5, using FO method estimation, the combination error model gives a better fit than the additive error model. The major PK parameter values, consistent with the ones estimated by iv, are correctly estimated. However, the bioavailability is higher than expected from previously published analyses and the central compartmental volume is less than estimated for iv and sc data; the variability on central compartment volume is high (64%).

The use of FOCE results in better estimation of the central compartment volume (25 L) and of the bioavailability (14%) compared to previously published data. Predictions vs. observations are better distributed on the

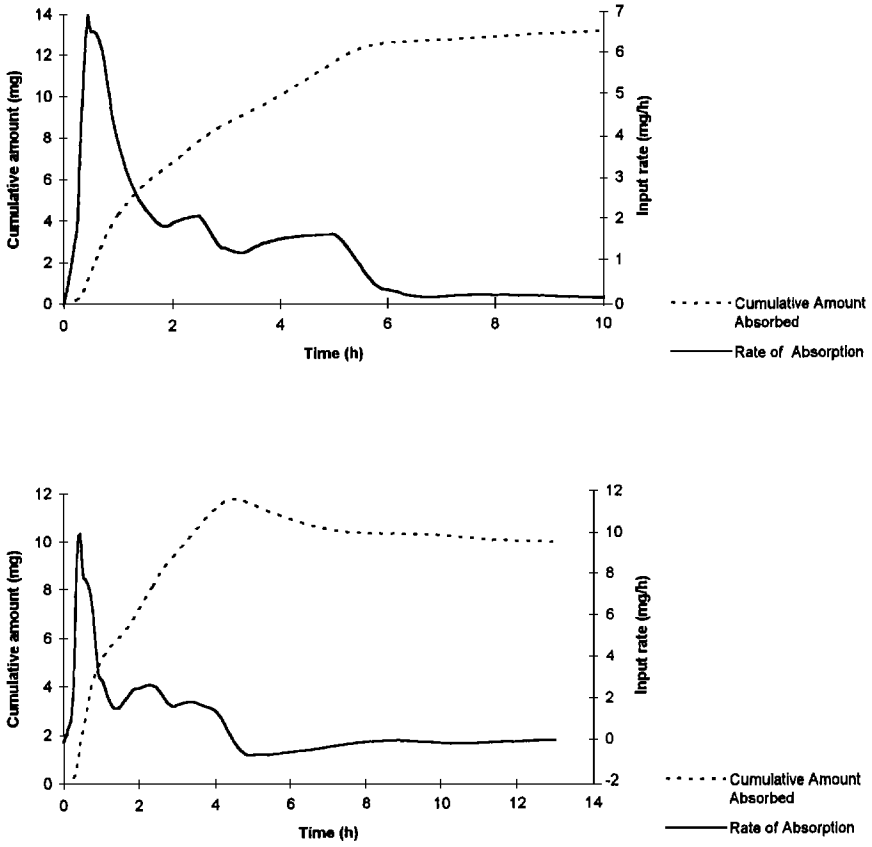

Fig. 4. Example of a deconvolution analysis for two typical subjects of Study B: Plots of cumulative amount and input rate vs. time. The input rate presents two phenomena, which can be described by a first-order and zero-order absorption processes.

unit line (Fig. 5). The total clearance is 68.7 L/hr, and the distribution volume at steady state is 109 L, resulting in an elimination half-life of 1.95 hr. The absorption parameters are the following:

For the first-order input:

$$ka = 0.667\ \text{hr}^{-1}; \qquad \text{lag time} = 0.227\ \text{hr}; \qquad f = 0.593$$

For the zero-order input:

$$D = 3.97\ \text{hr}; \qquad \text{lag time} = 0.483\ \text{hr}; \qquad f = 0.407$$

The absorption lasts 4.5 hr.

Table IV. Population Pharmacokinetic Parameter Estimates of Pooled Data, All Routes, and Healthy Subjects: Selection of the Structural Model[a]

Parameters	FO method				FOCE method	
	$Y = F + err$		$Y = F + err \cdot \sqrt{1 + \theta^2 \cdot F^2}$		$Y = F \cdot (1 + err)$	
Disposition						
CL (L/hr)	74.3	(1.7)	75.1	(2.44)	68.7	(1.34)
V (L)	7.57	(9.05)	12.3	(5.49)	24.7	(7.98)
Q (L/hr)	94	(5.44)	62.2	(6.21)	61.4	(3.55)
V_{SS} (L)	72.47	—	106	—	109	—
Absorption						
Ka (hr^{-1})	0.632	(6.16)	0.611	(6.4)	0.667	(5.35)
Lag time first-order (hr)	0.425	(2.49)	0.23	(1.85)	0.227	(1.55)
Duration (hr)	2.94	(0.54)	4.38	(1.03)	3.97	(0.55)
Lag time zero-order (hr)	1.99	(0.42)	0.486	(3.64)	0.483	(0.48)
F	0.155	(4.59)	0.213	(7.75)	0.14	(2.89)
f	0.834	(3.18)	0.622	(7.51)	0.593	(5.16)
Interindividual variability (CV%)						
ω_{CL}	14.3	(28.2)	18.8	(24.7)	14.8	(14.8)
ω_V	93.9	(17.2)	63.8	(12.5)	62.8	(20.7)
ω_Q	40.3	(22.8)	32.4	(24.1)	33.5	(31.1)
$\omega_{V_{ss}}$	38.3	—	29.7	—	29.9	—
ω_{Ka}	54.1	(17.5)	46	(22.2)	51.1	(16)
ω_F	32.2	(24.1)	35.6	(23.3)	28.1	(20)
Intraindividual error						
σ	26.6	(11.2)	0.345	(21.3)	23.5	(4.76)
θ	—		0.318	(12.5)		
Derived parameters						
$T_{1/2}$ (hr)	1.12		1.96		1.95	

[a]Numbers in parentheses = SE of estimates (%).

Covariate Effects: Demographic Parameters

The selection procedure using GAM was inconclusive. None of the covariates was selected by the GAM function, as all p-values were greater than 0.05. However, the plots of the partial residuals vs. the covariates (Fig. 6) suggest a nonlinear relationship between total clearance and age and height. The total clearance seems constant in young, tall subjects (age <40 years; height >180 cm). Clearance decreases in subjects over 40 years of age while it increases linearly with height up to 180 cm, and linearly with weight. The plots also suggest a nonlinear relationship between the Vd_{ss} and age: The volume is constant below 50 years of age and decreases with age over 50 years, while increasing linearly with height and weight. Each covariate entered individually into the NONMEM models for clearance and for volume resulted in significant effects. Age and height significantly affected

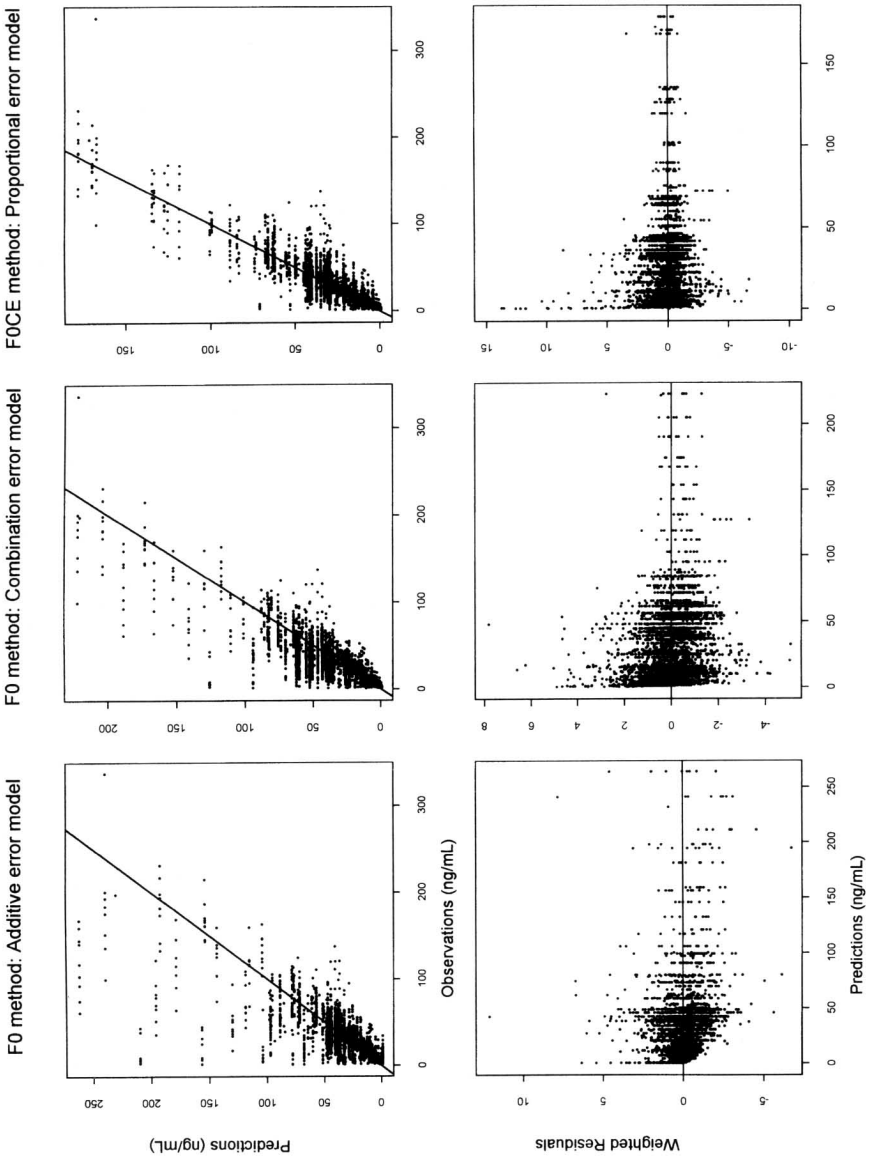

Fig. 5. Plots of predictions vs. observations and weighted residuals vs. predictions for pooled routes data after modeling with different intraindividual error models or using different estimation methods. The FOCE method and proportional error model combine better distribution of the points around the unit line of the plot of predictions vs. observations and better distribution of the points around the zero line of the plot of weighted residuals vs. predictions.

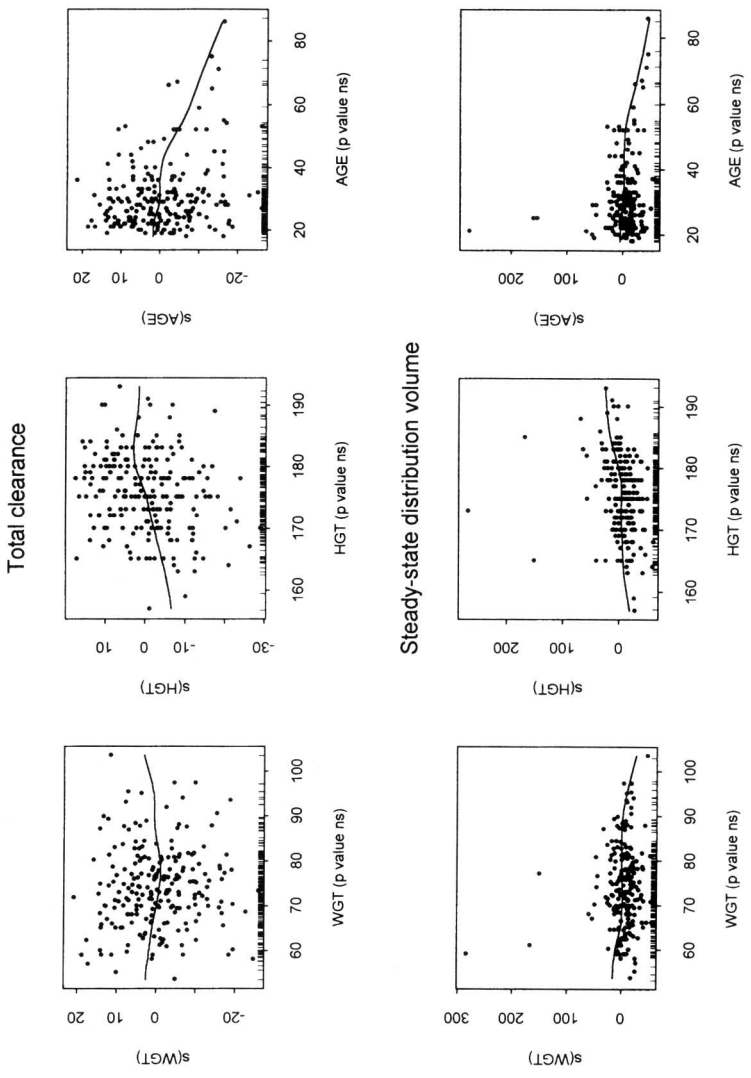

Fig. 6. GAM analysis for total clearance and distribution volume at steady state of the pooled routes data: Plots of the partial residuals vs. covariates. Each plot represents the contribution of a term to the additive predictor of the parameters.

clearance and volume separately. Final covariate models for total clearance and distribution volume at steady state were:

Total clearance model

$$CL = \theta_1 + \theta_2 \cdot (AGE^* - 40) + \theta_3 \cdot (HGT^* - 180)$$

where $\theta_1 = 80.5$ L/hr; $\theta_2 = -0.181$ L/hr/year, effect of age after 40 years (for $AGE > 40$ years); $\theta_3 = 0.993$ L/hr/cm, effect of height below 180 cm ($HGT < 180$ cm); and * = nonlinear relationship.

Distribution volume at steady-state model

$$V_{ss} = V + \theta_1 + \theta_2 \cdot (AGE^* - 50) + \theta_3 \cdot (HGT - 157)$$

where $V = 12.4$ L; $\theta_1 = 71.9$ L; $\theta_2 = -1.08$ L/year, effect of age after 50 years (for $AGE > 50$ years); and $\theta_3 = 1.33$ L/cm, effect of height.

In others words, the total clearance is constant and maximal, equal to 80.5 L/hr for young and tall subjects (age ≤ 40 years; height ≥ 180 cm). The clearance is less for older (age ≥ 40 years) and smaller (≤ 180 cm) subjects. The distribution volume at steady state increases continuously with height from 96.7 L in young subjects (age ≤ 50 years); the volume is less for older subjects (age ≥ 50 years). Since new generations tend to be taller than their parents are, in this older population we observe cumulative effects of short stature and greater age: decrease of total clearance and decrease of distribution volume at steady state.

The results are summarized in Table V.

Although significant, the covariates explain only 2.2% of the variability on total clearance (drop of 28 units in –2LL) and 3.4% of the variability on distribution volume at steady state (drop of 55 units in –2LL). Considering the low decrease of variabilities the full model was not investigated.

Covariate Effect: Migraine Effect

Two effects of the disease may affect the oral sumatriptan kinetics (i) "being a migraineur," even in a pain-free period (MIG, PF) and (ii) "being a migraineur during an attack" (MIG, MA). The structural model previously established in healthy subjects was fitted to two new data sets: healthy subjects and MIG, PF and healthy subjects and MIG, MA. The addition of effects of 'being a migraineur" was tested on all absorption parameters. Data from the same migraine patients collected during pain-free period and during an attack did not allow the comparison of full kinetics but only of the absorption parameters.

Effect of "being a migraineur" results in a drop of 100 units in –2LL for five additional parameters ($p < 0.0005$), three of them only being correctly estimated. Both lag times and the absorption duration were affected.

Table V. Effect of Covariates on Pharmacokinetic Parameters of Pooled Data, All Routes, Healthy Subjects[a]

Parameters	Covariate effect model[b]	
	$CL = \theta_1 + \theta_2 \cdot (AGEM - 40) + \theta_3 \cdot (HGTM - 180)$	$V_{ss} = V + \theta_1 + \theta_2 \cdot (AGEM - 50) + \theta_3 \cdot (HGT - 157)$
Difference in −2LL	28	55
p value	< 0.0005	< 0.0005
Disposition		
CL (L/hr)		
θ_1	80.5 (3.54)	74.8 (2.25)
θ_2	−0.181 (92.8)	
θ_3	0.993 (38.9)	
V (L)	12.5 (4.9)	12.4 (5.04)
Q (L/hr)	62.4 (6.52)	77.5 (6.49)
V_{ss} (L)		
θ_1	107.8 —	84.3 —
θ_2		−1.08 (44.4)
θ_3		1.33 (51.4)
Absorption		
Ka (hr^{-1})	0.644 (6.01)	0.615 (6.2)
Lag time first-order (hr)	0.235 (0.813)	0.23 (1.65)
Duration (hr)	3.85 (0.943)	4.38 (1.01)
Lag time zero-order (hr)	1.03 (0.158)	0.485 (3.03)
F	0.22 (7.36)	0.215 (7.67)
f	0.729 (4.4)	0.617 (6.97)
Interindividual variability (CV%)		
ω_{CL}	16.6 (25.6)	18.4 (23.8)
ω_V	62.9 (10.6)	63.3 (12.2)
ω_Q	32.9 (26.2)	32.7 (24.7)
$\omega_{V_{ss}}$	29.7 —	26.4 —
ω_{Ka}	45.9 (19.3)	45.8 (21.8)
Intraindividual error		
σ	0.338 (18.8)	0.332 (12.6)
θ	0.317 (11.4)	0.321 (23.2)

[a] Numbers in parentheses = SE of estimate/estimate (%).
[b] Model with additive intraindividual error using FO method.

Effect of MIG, MA results in a drop of 209 units in −2LL for five additional parameters ($p < 0.0005$), two of them well estimated: on lag time and zero-order absorption duration. Table VI presents the values of the absorption parameters in structural model and migraine effect model for both data sets. For the structural model, with any data sets, the parameters are very similar except that the zero-order absorption starts later for migraine patients during attack, suggesting gastric stasis. The negative effect of 'being a migraineur" on the duration of absorption merely reflects the sampling design, where no samples were collected after 4 hr postdosing. The migraine does

Table VI. Effect of Migraine Attack on the Absorption Parameters[a]

Parameters	"Healthy" structural model[b]		"Migraineur" model[b]	
	Healthy subjects and migraineurs PF[c]	Healthy subjects and migraineurs MA[c]	Healthy subjects and migraineurs PF[c]	Healthy subjects and migraineurs MA[c]
−2LL	20768	21107	20668	20898
Absorption				
Ka (hr^{-1})	0.589 (5.18)	0.533 (4.5)	0.542 (9.06) + MIG*0.0292 (>100)	0.554 (8.5) + MIG*0.0305 (>100)
Lag time first-order (hr)	0.223 (1.44)	0.227 (0.722)	0.231 (4.46) − MIG*0.0365 (26.7)	0.228 (1.15) − MIG*0.00511 (89.4)
Duration (hr)	4.28 (1.86)	3.93 (7.18)	4.01 (10.4) − MIG*0.811 (11.2)	4.4 (0.46) − MIG*1.19 (2.64)
Lag time zero-order (hr)	0.533 (1.23)	0.882 (30)	0.47 (9.04) + MIG*0.28 (18.2)	0.481 (1.57) + MIG*0.374 (6.68)
F	0.22 (5.64)	0.239 (11)	0.211 (5.88)	0.226 (9.38)
f	0.662 (6.16)	0.656 (6.88)	0.64 (10.3) + MIG*0.107 (96.3)	0.607 (5.98) − MIG*0.162 (89.5)

[a] Numbers in parentheses = SE of estimate/estimate (%).
[b] Model with additive intraindividual error using FO method. MIG flag coding for "being a migraineur" (for migraineur MIG = 1, for healthy subject MIG = 0).
[c] PF = during a pain-free period; MA = during a migraine attack.

not seem to affect the part of absorption described by first-order input, but rather the starting time of the zero-order input which is delayed in patients.

Simulations

Reduced data sets were obtained from the healthy subject population. Since not all the studies used the same time schedule, different optimal sampling times were defined. After oral route, the optimal sampling times were the following: 0.25, 0.5 hr, one sample between 2 and 3.5 hr, one sample between 5 and 7 hr, and the last sample when the concentration would be just above the limit of quantification. For intravenous or subcutaneous administrations, the optimal sampling times were the following: 0.33 hr, 0.3 hr, 0.75 hr, and one sample between 4 and 7 hr.

The structural model using FOCE fitted adequately the reduced data sets as shown on Fig. 7. The population parameters of both reduced populations were similar to those of the healthy subject population, full data set. The total clearance is equal to 68.9 L/hr after random reduction and to 73 L/hr after optimal reduction compared to 68.7 L/hr in the total population. The distribution volume at steady state is equal to 113 L after random reduction and to 127 L after optimal reduction compared to 109 L in the total population. The parameters obtained from randomly reduced data set are slightly closer to the total population parameters than the parameters obtained from optimally reduced data set, probably due to a better time scale description.

DISCUSSION

A large amount of data per individual puts constraints on the establishment of a mean population model and so is in opposition with an important interindividual variability. In this data-rich situation, the use of FOCE method with interaction, where the first derivatives of Taylor's series are evaluated at etas equal to conditional estimates, is strongly recommended. In fact, all our analyses showed a real improvement by using FOCE method compared to FO. The population PK parameters, clearance, absolute bioavailability, and distribution volume are in good agreement with results obtained previously by an individual noncompartmental analysis reported in literature (12,13). The intersubject variability on clearance is low at 15%, and the variability on distribution volume is equal to 30%. These results contradict previous reports of large intersubject variability of sumatriptan pharmacokinetics. The absorption model, with first-order input with lag time and zero-order input with lag time adequately describes all kinetic profiles observed in the studies of oral sumatriptan (2). The model has subsequently been used successfully to simulate different administration

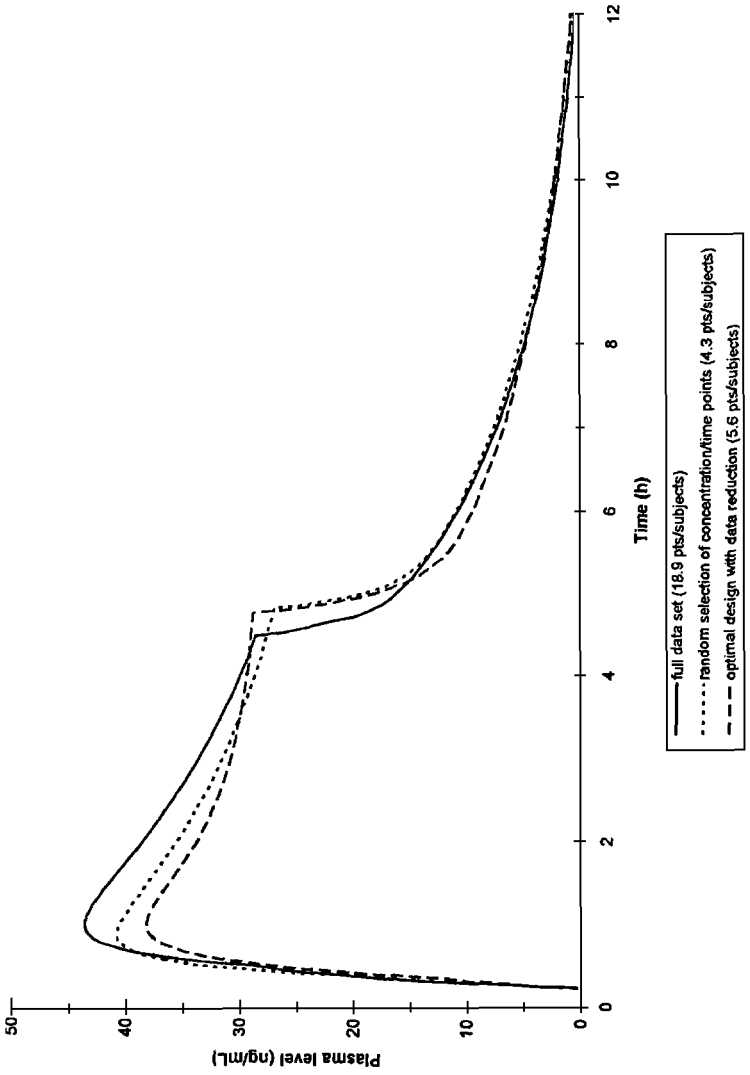

Fig. 7. Simulated sparse data scenarios: Population analysis of reduced data sets using the previous structural model.

regimen for common use in clinical setting and to analyze interactions between sumatriptan and other drugs (14).

The effect of age on clearance (a decrease of the clearance of 2 L/hr every 10 years) is very moderate and poorly estimated. This suggests that the clinical relevance of the effect of age is questionable. In fact, a pilot study conducted in elderly patients concluded the exposure to sumatriptan would not increase significantly at doses up to 3 mg sc and 100 mg po.

In a number of studies, weight has been shown to influence AUC and C_{max}. In this analysis, height instead of weight was found significant. Height and weight are usually associated to define the body size through relative weight index, body surface area, or the weight–height index (15,16). It is known that the sumatriptan elimination is mainly due to oxidative metabolism (80%) by the monoamine oxidase A isoenzyme (1,12). Since this enzyme is distributed throughout the body, given that this population did not include children or obese subjects, height is probably as good an indicator as weight of the distribution of the monoamine oxidase A isoenzyme.

Migraine attack has been associated with reduced rate of absorption of drugs, like aspirin or ergotamine, due to delayed gastric emptying and reduced motility (17,18,19,20). The absorption of sumatriptan in healthy subjects lasts 5 hr. The major effect observed in our analysis was to delay the zero-order absorption, whereas the noncompartmental analysis showed a slight decrease of AUC at 4 hr which was thought to be of no clinical significance (21).

Gender was not tested: There were only seven women in the healthy subject population, and the migraineur population, mainly female, did not provide useful information on clearance and volume. Hence, the migraine effect could not be separated from gender effect, although previous studies have shown that sumatriptan pharmacokinetics was not different between genders.

The initial development of sumatriptan used traditional individual approach, full kinetic profiles in healthy subjects, and few data in the target population. This retrospective population analysis highlights the lack of design in the data, which limited the analysis of covariates (gender or migraine effects) on PK parameters. In the global perspective of drug development, population kinetics has been proposed to conserve resources and to produce useful information for labeling. We have shown that resources conservation could be obtained through a better design and sparse sampling in Phase 1 studies to define the PK profile. Using the same number of studies, of subjects, and a total number of samples reduced to one quarter of its actual number, the parameter estimates were not different. Even with a PK model as complex as the one described above, it is possible to obtain

accurate estimates with much less data (4 to 5 concentration–time pairs per subject).

The studies selected for this retrospective analysis represent only a fraction of the total number of studies actually performed. Some addressed the absolute bioavailability of alternative oral formulations, others measured relative bioavailability; most of the studies were conducted in healthy young males. Several studies were open or so-called "pilot" studies. All provided limited labeling information.

Resources could have been preserved by conducting only studies to define the structural model e.g., absolute bioavailability of the market formulation, dose proportionality in a population closer to the target population (females). The determination of covariate effects used for dose definition (labeling) could have benefited from population modeling, had the criteria for inclusion/exclusion for Phase 2 to 3 trials been adapted to this approach. The kinetic data collected in the target population (migraineurs during an attack) were incomplete and hence inconclusive. Collecting fewer samples but with a better design would have allowed for the description of the full PK profile and helped to explain the flat oral dose response over the range of doses studied.

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