Modeling the Kinetics of Release of Octreotide from Long-Acting Formulations Injected Intramuscularly in Rabbits

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ABSTRACT: Long-acting repeatable formulations (LAR) based on polymeric microspheres were manufactured to deliver octreotide, an octapeptide analogue used in acromegaly. We developed a model to describe the complex triphasic concentration versus time profile observed in rabbits after intramuscular (im) injection of these LAR formulations. A 5-mg · kg^{-1} dose of octreotide in a reference LAR formulation was given im to eight rabbits; two groups of four rabbits each received a different formulation. In each animal, 26 blood samples were taken over 49 days. Concentrations of octreotide were assayed by radioimmunoassay. A model describing the concentration profile was developed. Octreotide release was described using the succession of an exponential model, a semiempirical non-Fickian model, and a delayed Weibull model. Parameters were estimated using nonlinear regression, first for the eight rabbits that received the reference formulation and then for the other eight animals. The model provides an adequate description of the concentration versus time profile for the three formulations. For the reference phase, erosion accounted for 87% of total drug release. The formulation encapsulating an octreotide–acetate complex showed a prolonged diffusion phase.
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Keywords: octreotide; long-acting repeatable; release profile; Weibull function; diffusion/erosion; mathematical modeling

INTRODUCTION

Octreotide is an octapeptide analogue of somatostatin, developed to normalize growth hormone levels.[1] Its main indication is acromegaly.[2] Long-acting repeatable (LAR) formulations (OncoLAR™, Sandostatin™, LAR™) were proposed, which markedly improve patient comfort: a single monthly intramuscular (im) injection is used instead of the thrice daily subcutaneous (sc) injection required during routine treatment. In a previous study using kinetic data from eight rabbits, obtained in a comparative study,[3] we derived the absorption profile of octreotide after im injection of a reference formulation of OncoLAR™ by deconvolution with respect to the disposition profile. We found that the concentration versus time profile was driven by the complex pharmacokinetics of release of the drug from a poly(DL-lactide-co-glycolide) glucose polymer (PLGA) matrix, and that the disposition was extremely fast (terminal half-life, 2 h). That analysis emphasized a triphasic pattern, both in the absorption profile and in

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the concentration versus time profile. Both drug diffusion through the matrix and polymer erosion combine to yield this pattern.

In the present study, we developed a model to describe the three successive phases apparent in the absorption profile. Drug diffusion has been studied using theoretical diffusion models[4,5] and semiempirical extensions.[6] Drug release from a surface-eroding structure was also described as a function of the geometry of the device,[7] but the more complex erosion in bulk has been studied using simulations[8,9] or recently by a model combining random and end-chain scission.[10] In the same field, a number of empirical models for drug dissolution have been developed.[11,12] To the best of our knowledge, no kinetic model describing a combination of erosion and diffusion processes has been applied to the whole *in vivo* profile of long-acting release drugs. Based on the previous theoretical works, we developed a general model to describe the physicochemical mechanisms of release of octreotide from long-acting formulation OncoLAR™. Estimates of the parameters were obtained by nonlinear regression, first in the eight rabbits of the previous study and then in two groups of four rabbits that received two formulations similar to the reference OncoLAR™, but with some manufacturing differences. We also tested for differences between the parameters in the different groups.

MATERIAL AND METHODS

Data

The data from the eight rabbits used to build the model have been described previously.[3] A 1-kg batch of the reference formulation of OncoLAR™ (formulation R in the following) was produced. Octreotide was manufactured by Novartis Pharma AG (formerly Sandoz Pharma AG), Basel, Switzerland; octreotide as pamoate salt (octreotide-pamoate) was encapsulated in microspheres of branched poly(DL-lactide-co-glycolide) glucose polymer (PLGA) (20% drug loading) according to a modified triple emulsion procedure.[13] After γ-irradiation (25–32 kGy) to sterilize the microspheres, the molecular weight (MW) of the polymer was found to be 40 600 $g \cdot mol^{-1}$. Microspheres of this formulation containing a 5-mg/kg body weight dose of octreotide were mixed within a vial with 1.5 mL of vehicle solution (phosphate buffered solution of pluronic and sodium carboxymethylcellulose containing benzyl alcohol, pH = 7.0), and injected im to eight 4-month-old male rabbits (strain: Chinchilla bastard; weight at delivery: 2.7–3.1 kg). Blood was collected 2 days before administration and at 10 and 30 min, at 1, 2, and 5 h, and at 1, 2, 5, 7, 9, 12, 14, 16, 19, 20 or 21, 21 or 23, 26, 28, 30, 34 or 33, 36, 41, 43, 47 and 49 days after administration. Octreotide was measured by radioimmunoassay.[1] The calibration curve showed coefficients of variation (CV) of 20% at 0.02 $ng \cdot mL^{-1}$ and of 10% at 2 $ng \cdot mL^{-1}$.

Two other formulations were used in this study. In both formulations, the polymer used as the constituant of the microspheres was identical. Four rabbits received a octreotide-pamoate formulation (Formulation P): this formulation was prepared exactly as formulation R, but the final MW of the polymer, which is dependent on the irradiation process, was slightly higher than the reference batch (MW = 42 300 $g \cdot mol^{-1}$), but remained within the range defined for quality control. Four other rabbits were given a second formulation (formulation A): in this formulation, octreotide is encapsulated as an acetate salt, and there is no irradiation after preparation of the microspheres, leading to a higher polymer weight (MW = 51 100 $g \cdot mol^{-1}$), and drug loading was lower (4.5%). For these two groups of four animals, the same protocol and analytical method prevailed.

Model

The model that describes the concentration versus time profile [$C(t)$] required the specification of several submodels; they are, release of the drug from the polymeric carrier at the site of injection, absorption from this site into the central blood flow, tissue distribution, and elimination of the drug. In the previous analysis, we studied the disposition kinetics of octreotide after intravenous (iv) injection. The rate constants of distribution and elimination estimated in that work indicated that disposition processes were very fast compared with the time scales of the different release processes, as seen in the concentration versus time curves.[3] In the present study, we focused on the mechanisms of drug release.

Figure 1 is a schematic diagram of the model we developed in which each process was assumed to contribute to a fraction of the total release. In this model, $R_i(t)$ (i = 1, 2 or 3) is the amount of drug released from the microsphere through process i up to time t into a volume V_i inside the muscle. The concentration of drug in muscle at

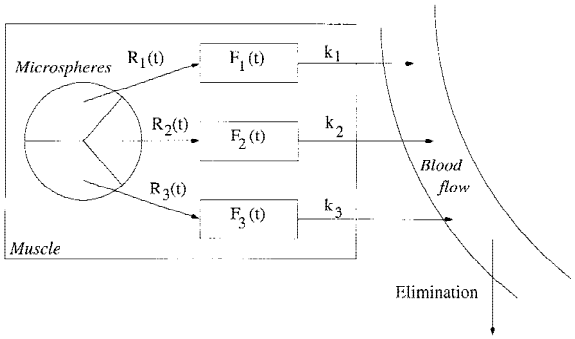

Figure 1. Diagram of the different components of the model for drug release. Microspheres are injected in the muscle and the drug released in three fractions.

time t due to process i, termed $F_i(t)$, was assumed to be absorbed into the blood according to a first-order process with rate constant k_i. This process obeys the following differential equation:

$$\frac{dF_i(t)}{dt} = \frac{1}{V_i}\frac{dR_i(t)}{dt} - k_i F_i(t) \quad (1)$$

The amount of drug arriving into the blood flow per unit time is then $\Sigma_{1\le i\le 3}\, k_i\, F_i\, V_i$. Let k be the elimination rate of octreotide from the body. The concentration of octreotide, $C(t)$, follows the following differential equation:

$$\frac{dC(t)}{dt} = \sum_{i=1}^{3}\frac{V_i}{V_b}k_i\, F_i(t) - kC(t) \quad (2)$$

Because disposition is very fast, the absorption of octreotide from muscle into blood flow can be seen as the limiting step, and therefore we can write the following approximation for $C(t)$:[14]

$$C(t) = \sum_{i=1}^{3}\frac{V_i}{V_b}\frac{k_i}{k}F_i(t) \quad (3)$$

We described the different R_i according to the underlying mechanism of release. The first phase consists of a transient release of drug from or close to the surface as the microspheres soak in water. We described this phase using the exponential model, the simplest sigmoid model, because this phase reflects the dissolution of the drug close to the surface of the microspheres and the shape of this peak did not suggest a diffusion model. Let D be the total dose of octreotide administered, α_1 be the fraction of drug released through this process, and β_1 be the rate constant of the initial exponential release:

$$R_1(t) = \alpha_1 D\,(1 - e^{-\beta_1 t}) \quad (4)$$

During the second phase, the drug was released from the polymeric matrix by diffusion, and the fraction released was modeled using the semiempirical non-Fickian model developed *in vitro*.[6] Let α_2 be the fraction of drug released through this process, γ_2 be the non-Fickian coefficient, $T_{f,2}$ be the time at which fraction 2 has completely diffused:

$$R_2(t) = \begin{cases} \alpha_2 D\left(\dfrac{t}{T_{f,2}}\right)^{\gamma 2} & \text{for } t \le T_{f,2} \\ \alpha_2 D & \text{for } t > T_{f,2} \end{cases} \quad (5)$$

Octreotide release during the third phase occurs as a result of polymer erosion. Hydrolysis starts when the microspheres are hydrated; the polymer chains become soluble at a MW of <5000 Da, releasing the remaining drug.[15] *In vitro* dissolution data could be modeled according to a Weibull function; therefore, we chose a delayed Weibull function to describe the erosion process. The parameters are α_2, the fraction of drug released during this last phase; β_3, the rate constant of the Weibull process; γ_3, the sigmoidicity constant; and $T_{lag,3}$, a lag-time corresponding to the time at which the polymer chains become soluble, allowing drug release:

$$R_3(t) = \alpha_3 D\left(1 - e^{-\left(\frac{t - T_{lag,3}}{\beta_3}\right)^{\gamma_3}}\right) \quad (6)$$

In the eqs. 1–3, the parameters V_i, V_b, and k were not identifiable because there was no data inside the muscle. We therefore defined new constants $\alpha_i^* = \alpha_i/(V_b k)$ to keep the model identifiable. As can be seen by taking the integral of eq. 3, the estimated α_i^* represents the area under the curve (AUC) for each process for a unit dose (we expressed the values in units of days/L). The AUC of each process is therefore the dose (~15 mg) times α_i^*. The fractions $\alpha_i^*/\Sigma_{1\le j\le 3}\alpha_j^*$ can be used to compare the relative importance of the different processes.

Statistical Analysis

The concentration versus time data from each animal were analyzed separately using nonlinear

regression. An additive zero mean normal heteroscedastic error (ϵ) was assumed, and errors on observations at different times were considered to be independent. Error variance was modeled as a quadratic function of the estimated concentration (C), according to the calibration curve: $\text{var}(\epsilon) = (0.002 + 0.1C)^2$. For each model, the nls2 program,[16] implemented in the Splus language,[17] was used to numerically integrate the differential equations from time zero, with initial conditions $F_i(0) = 0$, and to estimate the parameters by maximum likelihood. The values of $T_{\text{lag},3}$ and $T_{\text{f},2}$ could not be estimated using the same approach because they represent changepoints in the model.[18] The following procedure was used for each rabbit: for $T_{\text{f},2}$, a set S_2 of 15 values centered on the observed T_{max} of the second peak was constructed; for $T_{\text{lag},3}$, the set S_3 of 15 values centered on the value obtained by graphical analysis of the spline representation for the third peak was constructed. The spacing between two different points was 0.5 (day) for both sets. For each couple ($T_{\text{f},2}$; $T_{\text{lag},3}$) belonging to the grid $S_2 \times S_3$, nonlinear regression was performed fixing the two time parameters. The couple ($T_{\text{f},2}$; $T_{\text{lag},3}$) for which the lowest log-likelihood was found was selected. Assuming that the likelihood function is continuous, the precision for $T_{\text{lag},3}$ and $T_{\text{f},2}$ is 0.5, but could be decreased by smaller spacing.

To test the assumption of different k_i, we then successively fitted three models for each animal, one in which different k_i were used, one in which $k_1 = k_2 = k_3$, and one in which $k_2 = k_3$ but with a different k_1. A log-likelihood ratio test was used to select the best model.

Nonparametric tests were performed to explore the differences between formulations. Using the individual estimates, a Wilcoxon rank test was performed for each parameter to detect whether it was significantly different from the reference formulation. Indeed, release occurs through the same mechanisms but the relative contribution of the different processes to overall profile may vary according to manufacturing differences or the characteristics of the salt complex.

RESULTS

The parameters of the model were first estimated in the eight animals that had received the reference formulation. Figure 2 shows a plot of the concentration versus time profile predicted and observed for a typical animal. In this animal, the estimated parameters were the following, with associated standard error of estimation in brackets: $\alpha_1^* = 0.04\ 10^{-3}$ day/L ($0.01\ 10^{-3}$), $\beta_1 = 49.45$ day^{-1} (14.29), $k_1 = 5.76$ day^{-1} (1.68), $\alpha_2^* = 0.88\ 10^{-3}$ day/L ($0.05\ 10^{-3}$), $\gamma_2 = 0.97$ (0.11), $T_{\text{f},2} = 5$ days, $k_2 = 0.29$ day^{-1} (0.03), $\alpha_3^* = 8.27\ 10^{-3}$ day/L ($0.40\ 10^{-3}$), $\beta_3 = 13.33$ days (0.30), $\gamma_3 = 5.16$ (0.29), $T_{\text{lag},3} = 9$ days, $k_3 = 0.19$ day^{-1} (0.01). In the eight animals, plots of the weighted residuals showed a good adequacy of the model for all three processes. For two animals, the data did not allow good estimation of the parameters of the first two phases. The coefficients of variation of the estimation errors for these two peaks ranged from 7 to 70% excluding these animals. For the third phase, the coefficients of variation were <20% in all animals. This result also reflects that 15 data points provided information to estimate the parameters of this third phase, whereas there were only 10 to 11 measurements providing information on the seven parameters involved in the two first phases.

Table 1 displays a summary of the parameters estimated in the eight animals, computed with a standard two-stage approach from the individual estimates. Figure 3 shows the pooled octreotide concentrations measured in the eight animals, along with the curve predicted by the model using the mean parameters estimated by individual nonlinear regression. The standard deviations shown in Table 1 quantify the interindividual variability of the different parameters. The very low estimated variability in α_3^*, in contrast to the variabilities on the parameters estimated for the other phases, indicates a consistent amount of drug released during the final phase. In this formulation, the fraction of drug released through erosion of the polymer is 87%. This amount is consistent with the previous nonparametric analysis where we found, using spline functions to represent each fraction released, that the last phase represented 85% of total drug release.[3] We computed the area under the curve for the profile obtained using the mean parameters in Table 1 for a dose of 15 mg from the sum of the three α_i^*, and found an AUC of 139.07 mg $\cdot$ L^{-1} $\cdot$ day.

We tested whether the rate constant of absorption could be assumed identical across all three phases. The submodel with $k_1 = k_2 = k_3$ performed significantly worse than the model with different k_i ($p < 10^{-8}$), as did the model with $k_2 = k_3$ ($p < 10^{-6}$). As seen in Table 1, the estimated

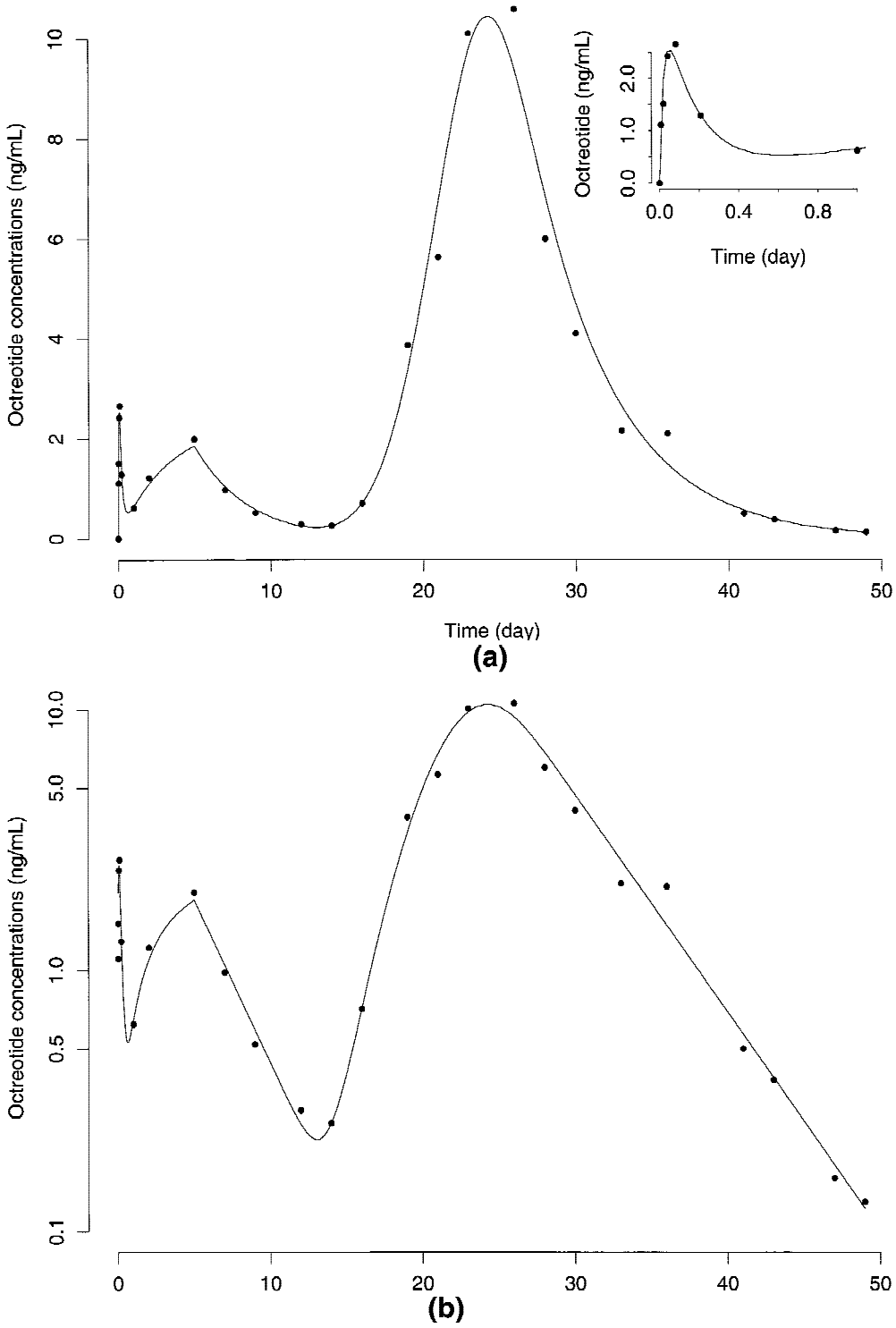

Figure 2. Time course of octreotide concentrations in a typical rabbit, after an im injection of 5 mg · kg^{-1} of the reference formulation (a) normal scale and (b) log scale. Experimental concentrations are symbolized by ●. Lines represent the concentrations predicted by the model. The inset in (a) shows a magnification of the concentrations observed and predicted during the first day after injection.

Table 1. Summary Statistics of the Parameters Estimated in the Eight Rabbits of the Reference Batch[a]

Parameter	Mean	SD	Min	Max
α_1^* (day/L)	$0.05\ 10^{-3}$	$0.04\ 10^{-3}$	$0.02\ 10^{-3}$	$0.14\ 10^{-3}$
β_1 (day)	96.38	82.23	11.75	269.76
k_1 (day^{-1})	5.22	3.06	1.32	11.41
α_2^* (day/L)	$1.08\ 10^{-3}$	$0.44\ 10^{-3}$	$0.62\ 10^{-3}$	$2.02\ 10^{-3}$
γ_2 (–)	0.89	0.38	0.09	1.31
$T_{f,2}$ (day)	3.9	1.5	2.0	5.0
k_2 (day^{-1})	0.26	0.09	0.13	0.44
α_3^* (day/L)	$7.81\ 10^{-3}$	$1.56\ 10^{-3}$	$6.05\ 10^{-3}$	$10.89\ 10^{-3}$
β_3 (day)	11.51	2.62	6.11	14.20
γ_3 (–)	5.04	2.34	2.83	10.35
$T_{lag,3}$ (day)	10.1	1.8	7.5	12.0
k_3 (day^{-1})	0.16	0.05	0.08	0.24
σ^2	1.76	0.39	1.35	2.32

[a] Mean, standard deviation, minimum, and maximum values are given. The parameters were estimated using a standard two-stage approach based on the individual estimates.

rate constants decreased from one phase to the other, which corresponds to a decrease of absorption rate with time.

The model was then applied to two other groups of four animals with different formulations. Figure 4 displays the fit of the model in one animal for each of these two formulations. Table 2 displays the parameters estimated in the two formulations, as well as the result of the Wilcoxon test. The second phase lasted longer in formulation P, although α_2^* was unchanged in formulation P. For formulation A, we found two main differences. First, the initial release was so rapid that it was impossible to estimate β_1, which we fixed to

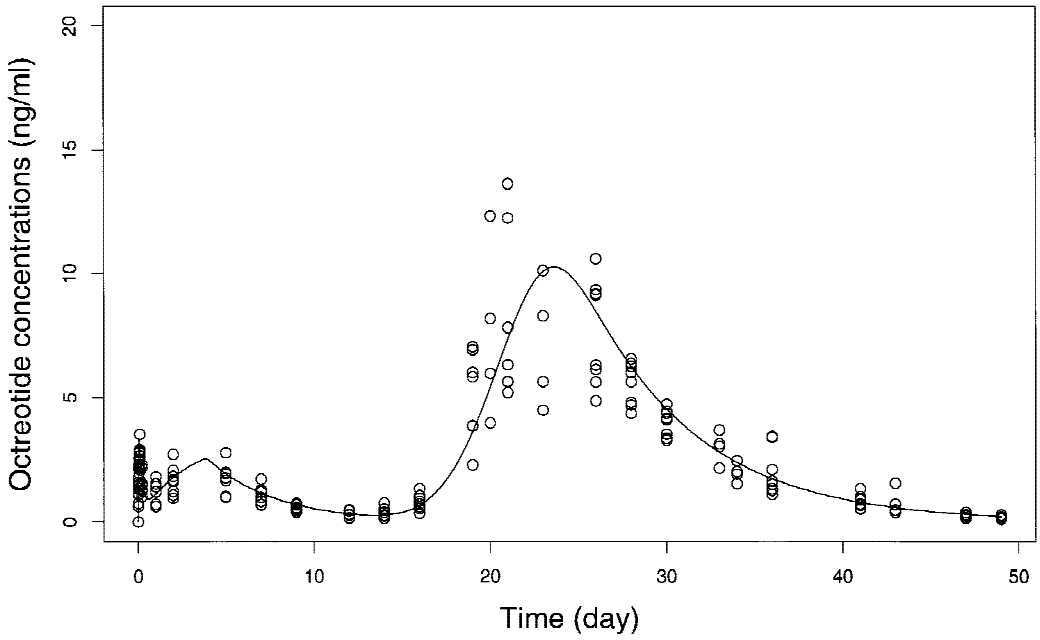

Figure 3. Pooled concentrations versus time measured in the eight animals after im injection of 5 mg · kg^{-1} of the reference formulations (○). The solid line is the time course predicted using the mean of the estimated individual parameters.

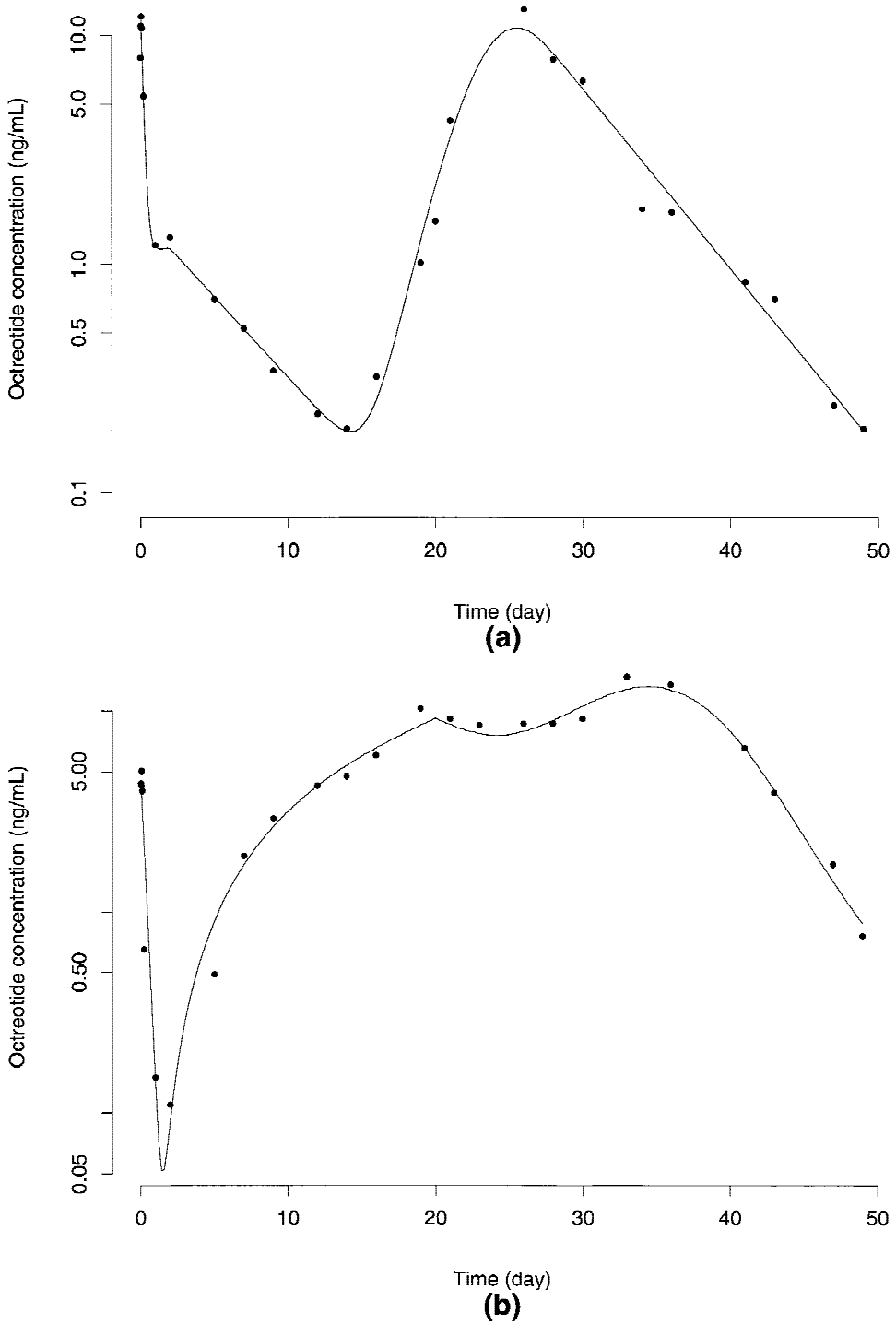

Figure 4. Time course of octreotide concentrations versus time in log scale in a typical rabbit after an im injection of 5 mg · kg^{-1} of (a) formulation P; (b) formulation A. Experimental concentrations are symbolized by ●. Solid lines represent the concentrations predicted by the model.

an arbitrarily high value. Second, a significant difference was found for all the parameters of the diffusion phase for this formulation. The diffusion phase is extended, as seen from the higher $T_{f,2}$, but the apparent amount of drug released through diffusion is smaller than for the reference formulation and it is negligible compared with that released through erosion.

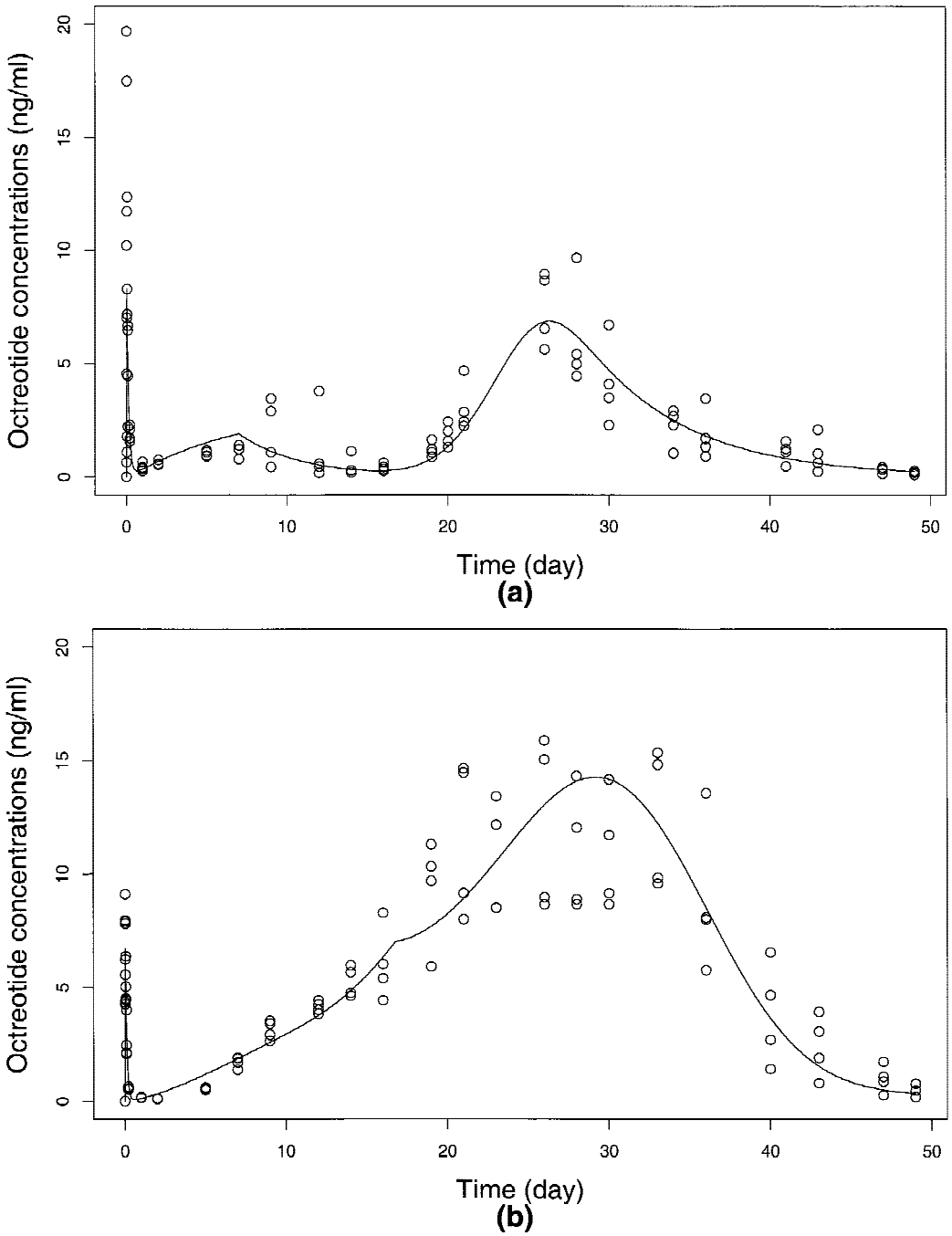

Figure 5. Pooled concentrations versus time (○), measured in four animals after im injection of 5 mg · kg^{-1} of (a) formulation P; (b) formulation A. The solid line is the time course predicted using the mean of the estimated individual parameters.

DISCUSSION

Theoretical models have been developed since 1961 to describe drug release *in vitro* from a variety of devices.[4,7] These models were based on stringent assumptions, because they described ideal conditions that were often far from experimental *in vivo* conditions. Because the situation was extremely complex, the case of bulk-eroding devices has only recently received elaborate treatment.[10] However, these theoretical models are often either poor approximations of situations en-

Table 2. Mean (and Standard Deviation) of the Parameters Estimated in Four Rabbits for Each of the Two Different Formulations A and P[a]

	Formulation P		Formulation A	
Parameter	Mean (SD)	p value	Mean (SD)	p value
α_1^* (day/L)	$0.08\ 10^{-3}$ ($0.03\ 10^{-3}$)	$p < 0.05$	$0.05\ 10^{-3}$ ($0.03\ 10^{-3}$)	NS
β_1 (day^{-1})	1652.25 (3050.61)	NS	10^4 (NA)[b]	—
k_1 (day^{-1})	8.08 (3.31)	NS	11.17 (5.14)	NS
α_2^* (day/L)	$0.98\ 10^{-3}$ ($2.82\ 10^{-3}$)	NS	$6.70\ 10^{-3}$ ($2.67\ 10^{-3}$)	$p < 0.005$
γ_2 (–)	1.20 (0.36)	NS	1.54 (0.17)	$p < 0.004$
k_2 (day^{-1})	0.26 (0.13)	NS	0.09 (0.01)	$p < 0.004$
$T_{f,2}$ (day)	7.0 (1.6)	$p < 0.02$	16.75 (3.2)	$p < 0.006$
α_3^* (day/L)	$5.39\ 10^{-3}$ ($1.81\ 10^{-3}$)	$p < 0.05$	$13.17\ 10^{-3}$ ($3.45\ 10^{-3}$)	$p < 0.008$
β_3 (day)	13.44 (1.48)	NS	21.67 (3.46)	$p < 0.004$
γ_3 (–)	5.46 (3.22)	NS	3.62 (1.45)	NS
k_3 (day^{-1})	0.16 (0.03)	NS	1.24 (0.84)	$p < 0.004$
$T_{lag,3}$ (day)	10.75 (1.5)	NS	9.1 (2.1)	NS

[a] These parameters were compared with those estimated in the reference formulation using a Wilcoxon rank test.
[b] Fixed; NA: not available.

countered in practice or too complex to be actually used in an experimental setting where data are sparse or measurements *in situ* are difficult to obtain. The present study is therefore, to our knowledge, the first model built to describe such complex *in vivo* data.

Our model describes the release of octreotide from the reference formulation OncoLAR™. The bulk of drug release occurred through polymer erosion during the third phase; this process was well characterized using the Weibull model, as shown by the small standard errors of estimation in all animals. S-shaped curves, such as the Weibull model, have been shown to characterize the release of encapsulated drug through dissolution processes.[11] Kervinen and Yliruusi[12] proposed an interpretation of the parameters of this class of model in terms of probability of dissolution. In a homogenous matrix, the differential equation for the fraction undissolved at time t is first order, with a factor $s(t)$ representing the average probability of dissolution. When $s(t)$ is constant, the solution of this differential equation is the exponential model. With other forms of $s(t)$, it yields various S-shaped profiles; examples are provided with $s(t)$ being a linear or quadratic function of time.[12] The Weibull model can be obtained with a power function of time $s(t) = \beta t^{\gamma-1}$. Dissolution data were obtained for the reference formulation via standard dissolution test apparatus, and the dissolution curve was also Weibull-shaped. However, because release of octreotide from the device in physiological medium is too slow, the dissolution medium was modified to allow almost complete release in 24 h. In these nonphysiological conditions, it is impossible to distinguish the contribution of the different release processes, and variability is limited by the use of identical cells. Therefore, as already pointed out by Bodmer et al.,[13] satisfactory *in vitro/in vivo* correlations have yet to be established.

The erosion peak was quite reproducible from one animal to the other. There was a rather high interindividual variability for the parameters of the first fraction released α_1^*, β_1, and k_1. This variability did not appear in the raw data shown in Figure 3, and it may be due in part to the estimation procedure. The two-stage approach was used because we had individual data with a relatively large number of measurements per animal. However, the large standard errors found for some animals for the first two phases may lead this two-stage procedure to overestimate the interindividual variability. Nevertheless, the objective of the study was to develop a model, and the complexity of the system prevented us from running a population analysis. Finally, the first two phases account for only a fraction of the main erosion process: the majority of drug is released during the last phase, as indicated by the value of α_3^*.

We found that the absorption rate decreased

with time; this result is reflected in the model by three different rate absorption constants for each of the three phases. A possible explanation for this decrease is progressive tissue encapsulation. The parameter k_1 is then probably the true rate of absorption from muscle to blood. This is consistent with the fact that this parameter does not significantly differ across formulations, as would be expected because octreotide, once released, should be absorbed identically notwithstanding the release process. In this study we modeled the time dependency by using three different rate constants, but it could be worthwhile to model explicitly the time dependency by using a rate constant changing linearly with time.

The model was developed also to provide a basis for formulation comparison. As illustrated, the model proved flexible enough to accommodate quite dissimilar profiles: a submodel with a fixed very high β_1, similar to an iv bolus, was fit to the data from formulation A because the release of the first fraction appeared to be complete before the first sampling in the animals. In the present study, nonparametric tests were carried out on the parameters found through individual estimation for the different formulations. We did not perform a correction for multiple tests because these corrections are often too conservative to allow detection of a difference. Nonetheless, differences between formulations could be investigated. We found small differences between formulations P and R. We also found differences in the diffusion process for the acetate-based formulation A with respect to the reference formulation. This result reflects the difference in the concentration profile, suggesting that physicochemical changes in the octreotide–salt complex and in the microsphere structure modified the diffusion of the drug from the polymer, and therefore the release profile (see Figure 4b). The disposition of the two salt forms of octreotide is, however, identical once the complex is in solution. This exploratory approach will need to be refined, using for example a population analysis including both formulations.

Formulation A has been used extensively in clinics, and it has demonstrated both efficacy and safety in acromegalic patients, as shown by Stewart et al.[19] The effect on growth hormone parallels exactly the octreotide concentration, and a single im injection once a month has been shown to control the growth hormone level in the eight patients of that study for several weeks. The efficacy has since been confirmed in larger studies. In long-term therapy, a new injection of octreotide-LAR is given while the previous one is still in the erosion phase to ensure that octreotide concentrations continuously remain above a threshold concentration. The model describing the release of octreotide from long-acting formulations will be used to analyze data in patients. The reference formulation described in the present paper was developed to allow higher drug loading, and it will also be administered in patients. The triphasic profile observed in the reference formulation would probably require modifying the administration to account for the shorter erosion phase. Modeling should enable us to predict the concentration levels and therefore to propose an optimal dosing regimen.

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