A Population Analysis of Nebulized (R)-Albuterol in Dogs Using a Novel Mixed Gut-Lung Absorption PK-PD Model[1]

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Purpose. The objectives of this study were to 1) construct a pharmacokinetic-pharmacodynamic (PK-PD) model, and 2) determine the PKs and PDs of (R)-albuterol when given by nebulization to 8 dogs for 7 consecutive days.

Methods. Four doses were evaluated (0.002, 0.02, 0.1, and 0.4 mg/kg/day). Blood samples were obtained after drug administration on days 1 and 7. Heart rates (HR) were obtained during treatment days 1, 4 and 7. All (R)-albuterol plasma concentrations were fitted using a mixed gut-lung absorption 2-compartment PK model. Day-1, 4, and 7 HR data were co-modeled using a direct response model with Hill-type equations, including a necessary tolerance phenomenon. The population PK-PD analysis was performed with an iterative 2-stage methodology (IT2S).

Results. No chiral inversion was seen, and double absorption peaks on the plasma concentration versus time curves were observed in the majority of dogs. These were hypothesized to be the result of combined gut and lung absorption of (R)-Albuterol. Results indicated that 67% (range: 57–89%) of (R)-albuterol systemic exposure after nebulized administration is due to gut absorption. Mean population PK parameters were KaGI (10±5.7 h^{-1}), KaLUNG (21±9.5 h^{-1}), CLc/F (0.6±0.2 L/h/kg), CLd/F (1.4±0.5 L/h/kg), Vc/F (1.4±0.9 L/kg), and Vp/F (4.8±2.4 L/kg). (R)-albuterol administration was associated with an increase in the dogs heart rates. A tolerance effect related to the cumulative dose was observed and modeled.

Conclusions. The presented PK-PD model appears to differentiate gut from lung absorption when (R)-albuterol is given by 15-minute nebulization to dogs. These results agree with the accepted hypothesis that most of the systemic exposure of (R)-albuterol after nebulized administration is due to gut absorption.

KEY WORDS: (R)-albuterol; enantiomer; population pharmacokinetic analysis; pharmacodynamics; nebulization.

INTRODUCTION

Albuterol is used for the treatment of a variety of lung diseases associated with airflow obstruction (1). Although marketed as a racemic mixture, only (R)-albuterol, a potent β_2-adrenoreceptor agonist, is thought to be responsible for most of the bronchodilator activity while (S)-albuterol has been implicated as being more toxic (2–4). Enantiomeric separation is a practice increasing in popularity, since a single isomer may represent a safer and a more efficacious alternative to its corresponding racemate (5). Inhalation is often the preferred route of administration for β_2-agonists since their therapeutic effects can be rapidly achieved with minimal systemic side effects (1,6). To our knowledge no information regarding the pharmacokinetics and the relationship between concentrations and pharmacologic response of nebulized (R)-albuterol has been published in the literature. The objectives of this study were therefore to 1) construct a compartmental pharmacokinetic and pharmacodynamic model describing the plasma concentrations of (R)-albuterol and the heart rate response after single and multiple nebulized administrations, and 2) derive population pharmacokinetic and pharmacodynamic parameters in dogs.

MATERIALS AND METHODS

Laboratory Procedure

(R)-albuterol was administered daily via nebulization to 8 Beagle dogs for 7 consecutive days. Four dosing groups (0.002, 0.02, 0.1, and 0.4 mg/kg/day) each composed of two dogs (one female and one male) were evaluated. The nebulized solutions of (R)-albuterol were administered using an oronasal face mask fitted over the dog's muzzle in such a way that the nose was inside the cylinder and the animal was mouth breathing through a small tube. Pari LC Plus nebulizers supplied with predried compressed air were utilized. Doses were given over 15 minutes. Blood samples were collected before, and at 0.08, 0.25, 0.5, 1, 2, 4 and 6 hours after drug administration on days 1 and 7. Heart rates were obtained at different times before, and during treatment days 1, 4 and 7 using limb lead II ECGs.

Analytical Procedure

(R)-albuterol plasma concentrations were determined by a previously published and validated HPLC method (7). The limit of detection was 125 pg/mL. Inter- and intra-day coefficient of variability of the analytical method ranged from 2 to 6% in terms of accuracy, while the recovery ranged from 87 to 112%.

Pharmacokinetic Analysis

Mixed Gut-Lung Absorption 2 Compartment PK Model

Compartmental pharmacokinetic techniques were used to analyse the data (8). Several classical PK models were evaluated (1, 2 and 3-compartment PK models) but rejected based on their inability to describe adequately the observed plasma concentrations of (R)-Albuterol. In particular, double absorption peaks were seen consistently and were hypothesized to be the result of combined gut and lung absorption processes. PK models including a dual absorption process were therefore constructed. Discrimination between candi-

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date pharmacokinetic models was performed based on visual inspection of graphs (concentrations versus time, weighted residuals versus observed concentrations) and computation of the Akaike's information criterion test. Construction of the most appropriate PK model was performed according to the law of parsimony. A 1-compartment PK model did not explained the observed plasma concentrations of (R)-albuterol as it consistently missed peak and trough concentrations. The PK model that simultaneously best fitted the observed Day-1 and -7 (R)-albuterol plasma concentrations was a linear mixed gut-lung absorption 2-compartment pharmacokinetic model. The pharmacokinetic parameters describing the model included: the percentages of the bioavailable dose of (R)-albuterol reaching the systemic circulation that were absorbed by the gut on days -1 and -7 (%GUT1, %GUT7), apparent central and peripheral volumes of distribution (Vc/F and Vp/F), one gut absorption rate constant (KaGI), one lung absorption rate constant (KaINH), apparent distributional and total clearances (CLd/F and CL/F), and two time-lags (Tlag1 and Tlag7). These time delays represented the elapsed time before the beginning of gut absorption on day -1 and -7. Their values were estimated during the preliminary population iterative processes. Once estimated with robustness, their value was fixed for each individual dogs and the population pharmacokinetic iterative process was restarted. The percentages of the bioavailable dose of (R)-albuterol reaching the systemic circulation via lung absorption on day -1 and -7 (%LUNG1 and %LUNG7) were obtained by subtracting the %GUT from 100%.

Pharmacodynamic Analysis

The relationship between the heart rate response and the plasma concentrations of (R)-albuterol was not characterized by hysteresis, indicating a fast equilibrium between plasma concentrations and the effective concentration of the drug at the biophase (theoretical site of activity). A pharmacodynamic model using a direct response with Hill-type equations (9) was therefore incorporated in the PK model. Initially, only the day-1 HR data was used to estimate the pharmacodynamic parameters Emax (maximal increase in HR by albuterol) and EC_{50} (concentration of albuterol associated with 50% of the maximal increase in HR) describing the model. The prediction of the day-7 heart rate data based on these values was however poor. All observed heart rates (day 1, 4 and 7) were therefore modelled by dosing groups and by treatment day. Results confirmed the apparition of a tolerance phenomenon with escalating doses and with time. This tolerance phenomenon appeared to correlate with the exposure of the drug, and therefore with the administered dose. The final PK-PD model is schematically illustrated in Figure 1. This model can be described with the following equations:

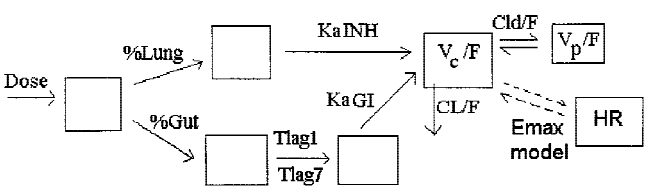

Fig. 1. Schematic representation of the PK-PD model.

$$\frac{dX1}{dt} := Z1 \cdot X5 - KaGI \cdot X1$$

$$\frac{dX2}{dt} := R(1) \cdot (1 - \%gut1) + (R(2) + R(3)) \cdot (1 - \%Gut7) - KaINH \cdot X2$$

$$\frac{dX3}{dt} := KaGI \cdot (X1 + X7) + KaINH \cdot X2 - \left(\frac{CLc + CLd}{Vc}\right) \cdot X3 + \frac{CLd}{Vp} \cdot X4$$

$$\frac{dX4}{dt} := \frac{CLd}{Vc} \cdot X3 - \frac{CLd}{Vp} \cdot X4$$

$$\frac{dX5}{dt} := R(1) \cdot \%Gut1 - Z1 \cdot X5$$

$$\frac{dX6}{dt} := R(3) \cdot \%Gut7 - Z2 \cdot X(6)$$

$$\frac{dX7}{dt} := Z2 \cdot X6 + R(2) \cdot \%Gut7 - KaGI \cdot X(7)$$

Where R(1), R(2), and R(3) represent the nebulized dose administered by a zero-order process on days 1, 2 to 6, and 7, respectively; and X(1) to X(7) are the amounts of drug in each boxes describing the model (1 to 7). Z1 and Z2 are "flag" parameters necessary for the coding of the day-1 and day-7 lag-times (Tlag1 and Tlag7). The observed plasma concentrations of (R)-albuterol (Y(1)) and heart rates (Y(2)) were fitted by the model using the following output equations:

$$Y(1) := \frac{X(3)}{\frac{Vc}{F}} \qquad Y(2) := HR_0 + \frac{HRmax\,Y(1)}{EC50 + Y(1)}$$

Where the HR_0, the HRmax, and the EC50 represent the baseline heart rate value, the maximum theoretical increase in heart rate above baseline, and the concentration associated with half of the maximum increase in heart rate, respectively. The tolerance model was the following:

$$EC_{50} := BaseEC_{50} + \left(\frac{MAXincr \cdot DOSE}{DOSE_{50} + DOSE}\right)$$

$$HRmax := 200 - \frac{60}{1 + \exp^{-g \cdot (DOSE - 2.25)}}$$

Where EC_{50} is a parameter which value starts at $BaseEC_{50}$ (in ug/L) and increases in a hyperbolic fashion depending on the cumulative dose (DOSE). The hyperbola is described by a Hill-type equation parameterized with a maximum increase (MAXincr) and a dose associated with half of the maximum increase ($DOSE_{50}$). HRmax is a parameter which value starts at 200 beats/min and decreases in a reversed hyperbolic fashion depending on the cumulative dose (DOSE). The parameters associated with this reverse hyperbola (200, 60 and 2.25) were obtained by modeling and were fixed. To describe the inward curvature of this decrease, the parameter g was estimated between dogs. Individual PK-PD estimates were derived using generalized least squares analysis with ADAPT-II (10) and were used as prior values for the population PK-PD analysis, which was performed with an iterative 2-stage methodology (IT2S) (11–13). All PK parameters were fitted para-

metrically assuming a normal distribution. Times to reach maximum plasma concentrations (Tmax) were noted directly from the data. All observations were fitted using a weighting procedure of $W_j = 1/S_j^2$ where the variance S_j^2 was calculated for each observation using the equation $S_j^2 = (a + b*Y)^2$ where a and b are the intercept and slope of each variance model. The residual variability (includes the intra-individual variability and the summation of all experimental errors) was therefore fitted with an additive proportional model where b is the slope and a is the intercept of each variance model (one for plasma concentrations Y(1) and the other one for heart rates Y(2)). Individual parameter estimates for this variance model were first estimated using generalized least squares analysis (ADAPT II) and were updated iteratively during the population PK analysis (IT2S). The parameters MAXincr and $DOSE_{50}$ were estimated among individuals during the initial population iterations, and were later fixed to a population value (MAXincr: 120 ug/L; $DOSE_{50}$: 0.5 mg/kg) once they were estimated with robustness.

RESULTS

Pharmacokinetics

No measurable concentration of (S)-albuterol was seen in the plasma following the administration of (R)-Albuterol in the 8 dogs studied, indicating a lack of chiral inversion. No relationship was seen between the observed areas under the plasma concentration time curves divided by the administered dose ($AUC_{0\text{-}T}$/dose) and the administered dose (Day 1: $R^2 = 0.07$, $p = 0.5$; Day 7: $R^2 = 0.01$, $p = 0.8$) indicating that the PK behavior of the drug was linear. In addition, all day-1 and day-7 plasma concentrations of (R)-albuterol were well fitted simultaneously within each dog using a linear PK model further suggesting that the PK behavior of the drug is linear (Fig. 2). No apparent difference was seen in the PK of the drug between male and female dogs.

Double absorption peaks were observed in the plasma concentration versus time curves of a majority of dogs, following the first and seventh daily doses of (R)-Albuterol. The first one was seen immediately following the end of the drug administration and was therefore hypothesized to result from the absorption of the drug from the lung tissue. The second peak was seen later (mean of 1.5 and 0.9h for days -1 and -7 respectively) and was therefore hypothesized to be the result of the absorption of the drug from the gut. Because of these two peaks, a conventional PK model with a single absorption constant was inappropriate at describing the PKs of the drug and consistently failed to capture the observed concentrations. Double peaks were seen 11 times while a single broader peak was apparent 5 times. In these instances, Tmax was observed on average at 0.5h on day 1 (n = 1) and day 7 (n = 4) following the end of drug administration.

The linear mixed gut-lung absorption 2-compartment PK model predicted the (R)-albuterol plasma concentrations very well. Goodness of fit was supported by the absence of

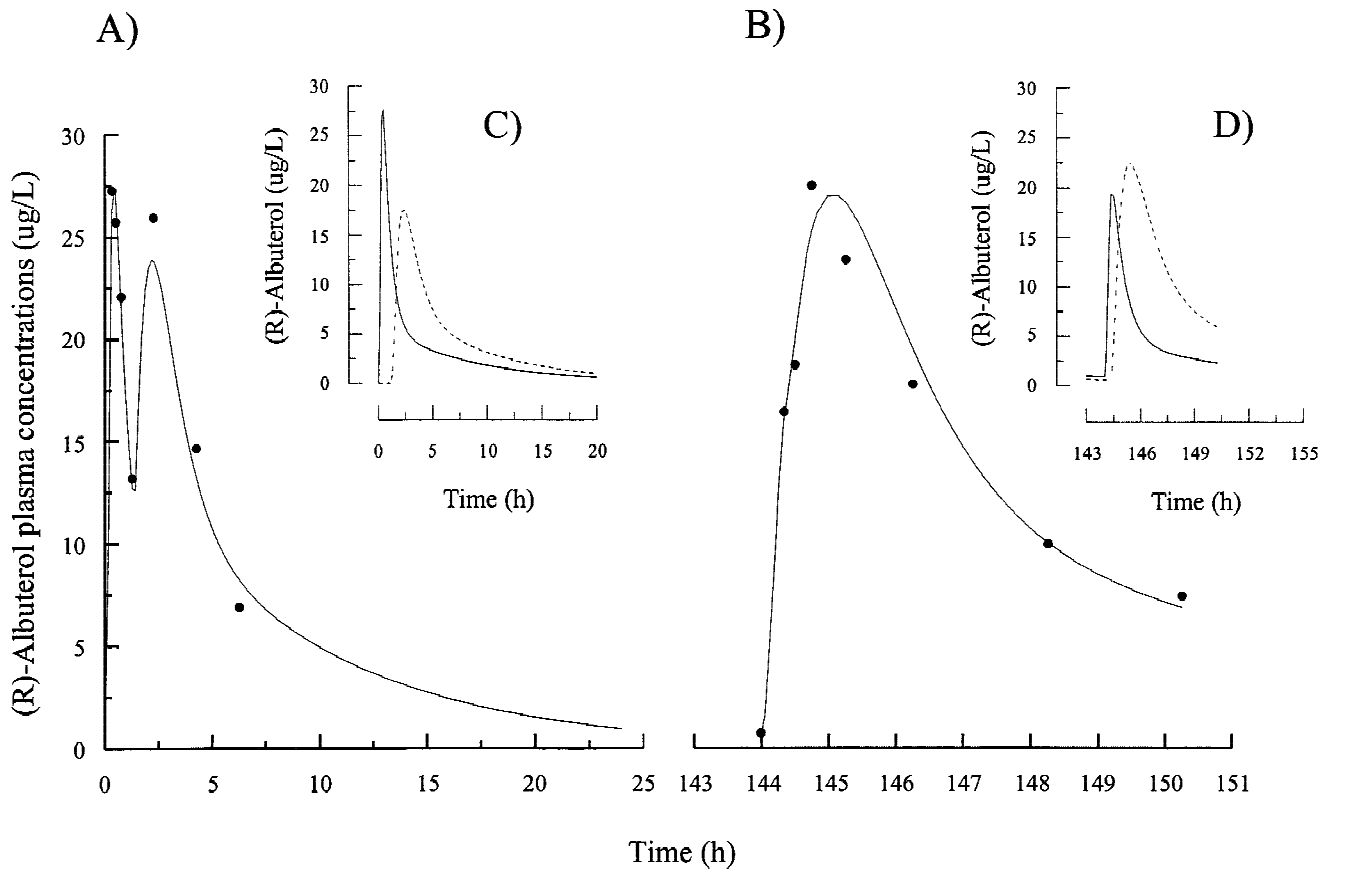

Fig. 2. Observed (•) and estimated (—) (R)-albuterol plasma concentrations versus time after 1 (panel A) and 7 days (panel B) of daily 15 minutes nebulized administrations of (R)-albuterol in a representative dog. Panel C and panel D represent the simulated (R)-Albuterol concentrations that are due to lung (___) and gut (....) absorption on day-1 and -7, respectively.

deviation on graphs of the weighted residuals versus observed (R)-albuterol plasma concentrations, and by a mean value of 0.92 for the coefficient of determination (R^2). Mean population PK parameter estimates are presented in Table 1). The mean (interindividual CV%) calculated percentages of the bioavailable dose of (R)-albuterol reaching the systemic circulation via lung absorption (1-%Gut) on days 1 and 7 were 32 (35) and 34 (39), respectively. The average calculated terminal elimination half-life for (R)-albuterol was 11 hours. The mean lag time before the start of the gut absorption on days 1 and 7 were estimated to be at 0.8 and 0.3 hours, respectively. Mean observed and fitted (R)-albuterol plasma concentrations versus time after 1 and 7 nebulized administrations are represented on Figure 2 for one representative animal.

Pharmacodynamics

The maximum increase in heart rate were observed at 0.9, 0.4, and 0.5h following the end of drug administration on days 1, 4, and 7, respectively. The average±SD baseline level for heart rate before drug administration was 143 ± 9, 123±9 and 118±9 beats per minute for day 1, 4 and 7 respectively. This difference may be a reflection of compensatory mechanisms in heart rate regulation, and/or due to the acclimation of the dogs to the experimental procedure.

The maximal percentage increase in heart rate following administrations of (R)-albuterol increased between dosages of 0.002 and 0.1 mg/kg/day but then decreased at the higher 0.4 mg/kg/day dosage (16, 43, 87 and 49% for daily dosages of 0.002,0.02,0.1 and 0.4 mg/kg/day respectively). This was indicative of a tolerance phenomenon. Based on pharmacodynamic parameters estimated with the day-1 data, the prediction of the day-7 data was poor also indicating a tolerance phenomenon. Heart rate was therefore modeled, in a preliminary analysis, by dosing groups and by treatment days. Results are presented in Table 2. It should be noted that these results are not to be considered definite and are likely to be affected by "noise", as only two dogs and one day of data were used to compute them. They are, however, sufficiently robust to indicate trends. For example, it is apparent that for the same treatment days the EC_{50} parameter increased with daily dosages above 0.02 mg/kg/day along with a doubling of its value between day-1 and -7. The EC_{50} value appeared therefore to be best explained by a Hill-type relationship against the cumulative dosages above a baseline value of approximately 5 ug/L (Figure 3, panel A). The HRmax value appeared to be best explained by a reversed Hill-type relationship against the cumulative dosages above a baseline value of approximately 200 beats/minute (Figure 3, panel B). The PK-PD model was therefore modified to include a tolerance phenomenon with the EC_{50} and Hrmax predicted by the different cumulative dosages, so that all data could be simultaneously modelled and explained.

The resultant linear mixed gut-lung absorption 2-compartment PK-PD model predicted the (R)-albuterol heart rate response very well. Goodness of fit was supported by the absence of deviation on graphs of the weighted residuals versus observed heart rates. Mean population PD parameter estimates were 4.2 ug/L and 3 (no units) for BaseEC_{50} and g, respectively. Mean observed and fitted (R)-albuterol heart rate response after 1 and 7 daily nebulized administrations are presented in Figure 4 for one representative animal.

DISCUSSION

The PKs of (R)-albuterol given by nebulization at doses ranging from 0.002 to 0.4 mg/kg/day was best described by a linear mixed gut-lung absorption two-compartment model. This is the first PK analysis describing the disposition of (R)-albuterol by a mixed absorption model. A linear two-compartment structural model was selected over a single compartment, as the plasma concentration-time curves of (R)-albuterol were characterized by a biphasic decay in all dogs. Two first-order absorption rate constants, KaINH and KaGI, were subsequently incorporated in the model. The addition of these two parameters was necessary, because double peaks, hypothesized to be the result of combined lung and gut absorption processes, were observed in the plasma concentration-time profiles of the majority of dogs studied on day-1 and -7 of therapy. These two peaks consistently appeared and were not a consequence of noise. This double rise in plasma concentrations has been previously described with the racemate salbutamol (14–16), and with several other agents of the class of β_2-agonists (17–19) after administration by nebulizers as well as by metered-dose inhalers. However, because these medications are racemic compounds, the observed double peaks could have been the result of different absorption profiles for the enantiomers. Enantiomers very often present different PKs and this has been previously demonstrated for (R)- versus (S)-albuterol (3,20). This is therefore the first pharmacokinetic model in which dual absorption processes are fitted simultaneously from the same administration of a single enantiomer. This model enabled us to estimate with good precision the proportion of the total systemic exposure which was due to gut versus lung absorption. Derks et al. have used a different strategy to fit the double peaks following the

Table 1. (R)-Albuterol Mean PK Parameter Estimates and Their Interindividual Variability (CV%) After Multiple Nebulized Administrations in Dogs

	Tlag1 (h)	Tlag7 (h)	%Gut1 (%)	%Gut7 (%)	KaGl (h^{-1})	KalNH (h^{-1})	CL/F (L/kg/h)	CLd/F (L/kg/h)	Vc/F (L/kg)	Vp/F (L/kg)
Mean	0.8 (*)	0.3 (*)	68	66	9.9	20.6	0.58	1.4	1.4	4.8
CV%	83	61	17	20	57	46	37	38	62	49

Note: %Gut1 and %Gut7 are the percentages of the bioavailable dose of (R)-albuterol reaching the systemic circulation that were absorbed by the gut on days 1 and 7, respectively; KaGl is the gut absorption rate constant; KalNH is the lung absorption rate constant; CLd/F and CL/F are respectively the distributional and the total clearances of (R)-albuterol; and Vc/F and Vp/F are respectively the central and the peripheral volumes of distribution. (*): Fitted values for each dog were fixed during the last population PK analysis.

Table 2. (R)-Albuterol Mean PD Parameter Estimates Based on Dosing Groups and Administration Days

Dosing groups (mg/kg/day)	Day 1		Day 4		Day 7	
	HRmax (beats/min)	EC50 (ug/L)	HRmax (beats/min)	EC50 (ug/L)	HRmax (beats/min)	EC50 (ug/L)
0.002 to 0.02	200	6	197	7.5	200	6
0.1	200	20	190	26	196	40
0.4	180	70	189	132	145	112

Note: HRmax is the maximum theoretical increase in heart rate above baseline; EC50 is the concentration associated with half of the maximum increase in heart rate.

administration of (R,R/S,S)-formoterol by inhalation (19). Each dose was split into two separate hypothetical administrations, one in the lung and the other one in the gut. The absorption constant governing the gut absorption was modeled in such a way that it did not influence the first peak. Specifically, the time-lag before the start of the gut absorption was the time where the two absorption peaks met on each individual concentration versus time curves. This assumes that the first absorption peak is only dependent on lung absorption and may therefore lead to an overestimation of the proportion of drug absorbed through the lung. They reported that 70% of the drug was possibly absorbed by the lung while being 30% absorbed by the gut. These figures are the inverse of what we have found: 68% of the bioavailable dose of (R)-albuterol was absorbed by the gut and the remaining by the lung. We believe that our proposed model allows a much better differentiation between gut and lung absorption because it is simultaneously fitted. However, the large difference seen between our two studies can also be the result of using (R,R/S,S)-formoterol instead of (R)-albuterol or because of a difference between dogs and humans. Nevertheless, our results indicate that most of the systemic exposure of (R)-albuterol after nebulized administration is due to gut absorption, suggesting that the majority of the bioavailable dose of (R)-albuterol given by inhalation is swallowed. When administering Teflon particles with pressurized aerosol canister

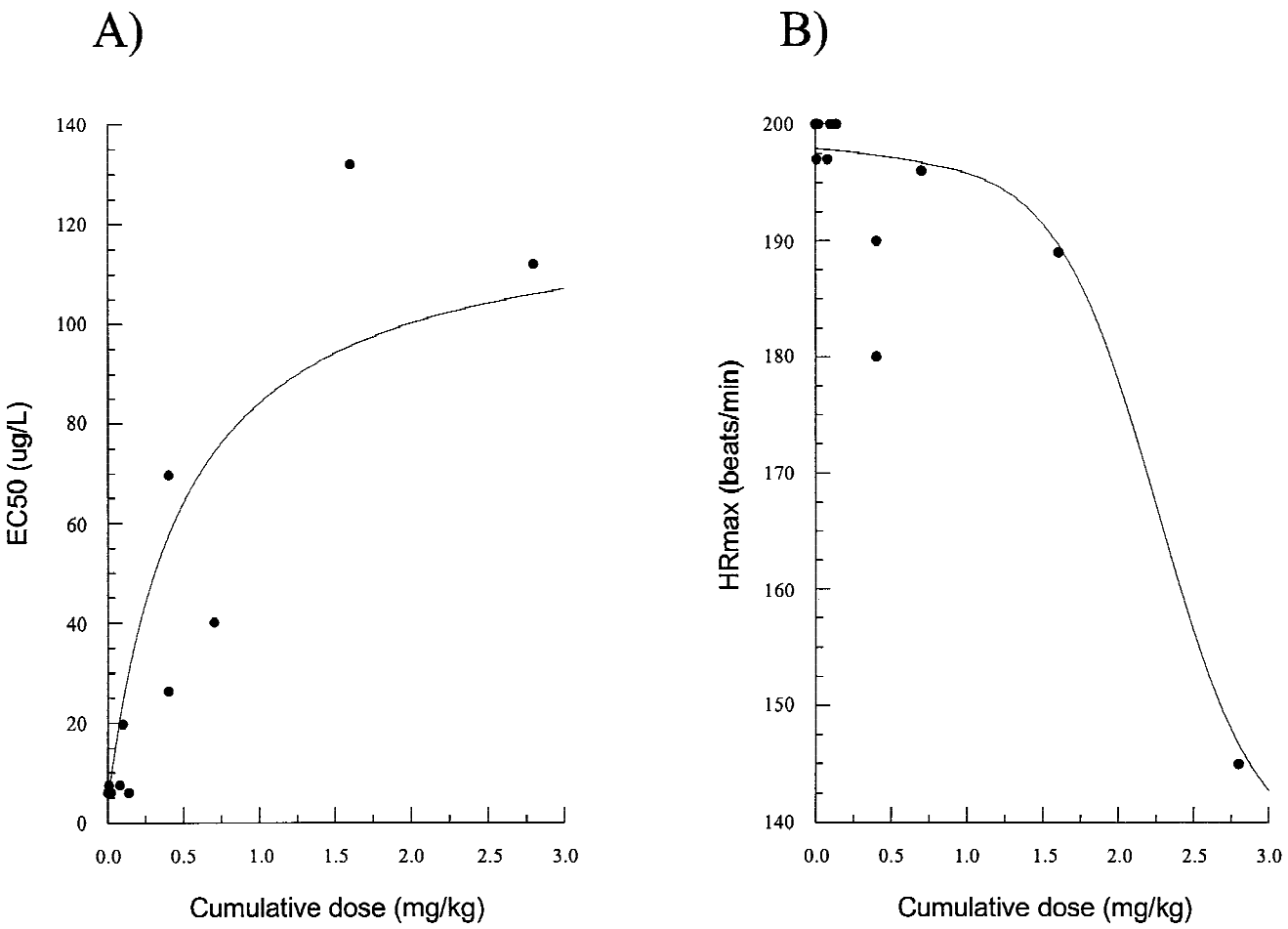

Fig. 3. Relationship between the preliminary estimation of EC_{50} and Hrmax PD parameters and the cumulative (R)-albuterol dose.

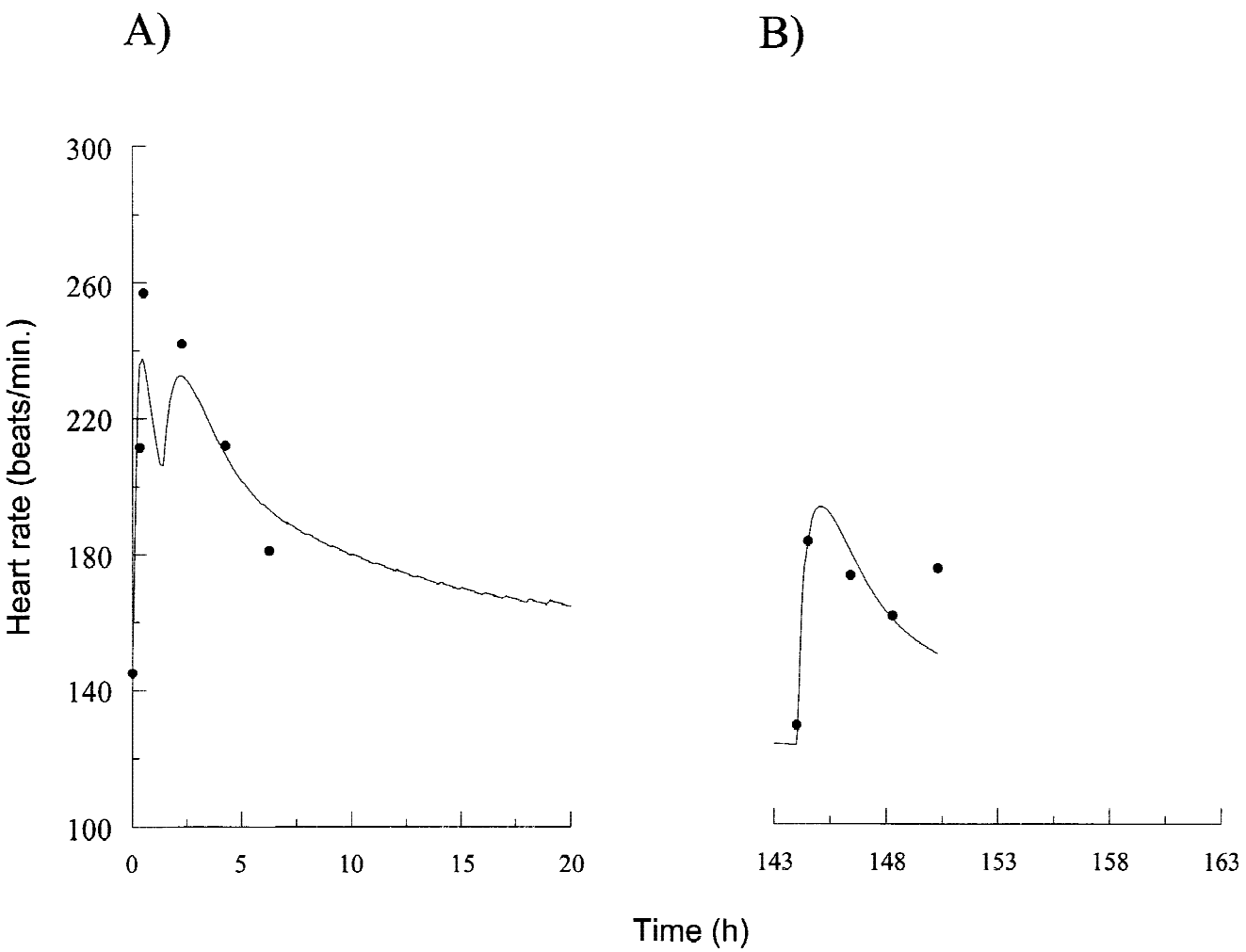

Fig. 4. Observed (•) and estimated (—) heart rates versus time after 1 and 7 days of daily 15 minutes nebulized administrations of (R)-albuterol in a representative dog.

to patients with obstructive airway diseases, Newman et al. found the deposition of the compound to be 10% in the lungs and 80% in the mouth, with the remainder of the dose either staying in the aerosol actuator or expired by the patient (21). Others have reported technetium-99m labelled salbutamol (albuterol) deposition in the lungs to be approximately 20% in patients using a metered dose inhaler with or without a spacer (22). These values are consistent with our findings in which approximately 30% of the bioavailable dose of (R)-albuterol is due to lung absorption. Other studies have also shown that the metabolic patterns of (RS)-albuterol and of its metabolites are the same in the plasma and urine whether the drug is administered orally or via pulmonary administrations (14,15,23). Because (RS)-albuterol undergoes extensive first pass metabolism in the gut (24–26), this observation is consistent with our results. Also, the time associated with the occurrence of our second absorption peak (1 hour) is comparable to the usual tmax seen for (R)-albuterol after its oral administration (2–3).

Two studies conducted by Boulton and Fawcett (2–3) have examined the PKs of the active enantiomer (R)-albuterol. The first one investigated the PKs of (R)-albuterol after intravenous and oral administrations of racemic albuterol in seven healthy volunteers (2). Evaluation of the enantiomeric disposition of albuterol was made possible by using a chiral HPLC assay with fluorescence detection. The calculated PK parameter values of (R)-albuterol following albuterol intravenous administration were CL (0.62 L/h/kg), CLr (0.32 L/h/kg), Vss (2 L/kg) and t1/2 (2 h). The values for the Vss and the t/12 are relatively low compared to the results reported in the present study which was undertaken in dogs instead of humans. Albuterol is metabolized to a sulphate conjugate in humans while it is mostly excreted unchanged in the urine in dogs (26–27). Because (R)-Albuterol was not administered intravenously in our study, we have reported the parameters Vss/F and CL/F and their values will therefore be higher than Vss and CL if F is less than 100%. Competitive inhibition between (R)- and (S)-albuterol has been described for the sulfoconjugation of albuterol, suggesting that the PK parameters calculated for (R)-albuterol after administration of the racemic mixture may differ from those obtained after the separate enantiomer administrations (28). This was confirmed by the second PK analysis performed by Boulder and Fawcett in 12 healthy volunteers in which single dose administrations of the racemic mixture and of the individual enantiomers of albuterol were compared (3). It was shown that the AUC of (R)-albuterol was significantly smaller after its own separate administration than after administration of the race-

mate. Distribution and elimination PK parameter values were not reported.

Administration of albuterol is known to increase heart rate. This is a normal pharmacological effect of β_2-receptor stimulation. In this analysis, albuterol administration increased heart rates in all dogs at all dosages studied. A tolerance was observed, however, with increasing cumulative dosages, i.e. increased concentrations of the drug were associated with a lesser than expected increase in heart rate. Similar findings have been reported when administering salbutamol by inhalation at doses ranging from 100 to 4000 ug to asthmatic patients (29), and when administering acutely and chronically different dosages of the drug to different breeds of pigs (30). A number of studies have been conducted to assess the potential development of airway tachyphylaxis from chronic administration of β_2-adrenergic agents. While most of the studies have found no significant loss of bronchodilatating effect, a few of the investigations have revealed a statistically significant decrease in effectiveness that is unlikely to be clinically significant. Tachyphylaxis to systemic effects of β_2-adrenergic agents such as tachycardia, hypokalemia, and hyperglycemia as well as down-regulation of β_2-adrenergic receptors of mononuclear blood cells appears to develop much more readily than does airway tachyphylaxis (29,31–34). In this study, we have tried to understand the relationship between this tachyphylaxis and the cumulative dosage of the drug. It appears that under a certain daily dosage (below 0.02 mg/kg/day) there is no tolerance phenomenon. Between 0.1 and 0.4mg/kg/day, however, the tachyphylaxis was best explained by the total cumulative dosage. It remains to be seen, however, if the proposed model would hold true for higher daily and cumulative dosages.

In conclusion, our results show that (R)-albuterol when given by nebulisation to dogs for seven days exhibit linear pharmacokinetics and does not undergo chiral inversion. Its pharmacokinetics was characterized by double absorption peaks which were hypothesized to be the result of gut and lung absorption. Using a novel PK-PD model we estimated the percentage of the bioavailable dose due to gut absorption to be on average 68%. The increase in heart rate following administration of higher doses of (R)-albuterol was less than predicted by the higher dosages, indicating a tolerance phenomenon. This tachyphylaxis appeared to be best correlated with the cumulative dose. In order to fully demonstrate its predictive ability , this proposed PK/PD model needs to be validated using a naïve data-set.

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