

## Regular article

## Population pharmacokinetic and pharmacodynamic modeling of epinephrine administered using a mobile inhaler

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## ABSTRACT

Inhaled epinephrine is a potential alternative to self-administered intramuscular epinephrine in imminent anaphylactic reactions. The objective was to develop a pharmacokinetic-pharmacodynamic model describing exposure and effects on heart rate of inhaled epinephrine. Data from a 4-phase cross-over clinical trial in 9 healthy volunteers including 0.3 mg intramuscular epinephrine, two doses of inhaled epinephrine (4 mg/mL solution administered during [mean] 18 and 25 min, respectively) using a mobile pocket inhaler, and an inhaled placebo were analyzed using mixed-effects modeling. Inhaled epinephrine was available almost immediately and more rapidly than via the intramuscular route (absorption half-life 29 min). Epinephrine plasma concentrations declined rapidly after terminating inhalation (elimination half-life 4.1 min) offering the option to stop exposure in case of adverse events. While the expected maximum concentration was higher for inhaled epinephrine, this was not associated with safety concerns due to only moderate additional hemodynamic effects compared to intramuscular administration. Bioavailability after inhalation (4.7%) was subject to high interindividual and inter-occasional variability highlighting that training of inhalation would be essential for patients. The proposed model suggests that the use of a highly concentrated epinephrine solution via inhalation may offer an effective treatment option in anaphylaxis, while efficacy in patients remains to be shown.

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## 1. Introduction

Anaphylaxis is potentially life-threatening and immediate treatment is mandatory [1]. The latest guidelines from the European Academy of Allergy and Clinical Immunology advocate 0.3 mg intramuscular adrenaline as first-line treatment [2]. For the outpatient management of anaphylaxis, autoinjectors are generally recommended. However, since many patients refuse the use of intramuscular epinephrine [3,4], a need for another rapidly acting route of administration has been identified [5]. Administration via inhalation represents a promising alternative with local activity and potentially rapid systemic absorption; however, results from different trials remain ambiguous concerning the efficacy of the investigated preparations of inhaled epinephrine [6–10].

Breuer et al. [5] explored pharmacokinetics and pharmacodynamics of moist inhalation epinephrine doses (4 and 8 mg of 1-

epinephrine in an aqueous solution of 4 mg/mL) relative to intramuscular and placebo inhalation. Inhalation was carried out by a battery driven mobile pocket inhaler (Taschenvernebler, Omron Microair U22). Based on standard non-compartmental analysis, the results indicated that epinephrine plasma concentrations and pharmacodynamic effects of inhaled epinephrine are at least not inferior to those following the recommended 0.3 mg epinephrine dose as i.m. injection, without causing relevant differences in the nature and severity of adverse effects [5].

However, models for predicting exposure and hemodynamic effects after inhalation are lacking. In the re-analysis presented here, the objective was to develop an empirical pharmacokinetic-pharmacodynamic model (PK/PD model) able to predict the expected bioavailability and the expected time course of epinephrine plasma concentrations with a direct link to the expected pharmacodynamic (in terms of heart rate) effects for different doses of nebulized epinephrine. Inter-individual variability should be quantified to estimate the expected variance in the population. Application of the model will allow for the optimization of the

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dosing strategy (i.e. duration of inhalation) regarding potential efficacy and adverse effects compared to the intramuscular reference.

## 2. Material and methods

### 2.1. Study design

This study was approved by the independent Ethics Committee of the Medical Association of North Rhine (Germany); written informed consents were obtained from all participants. Data was available from Breuer et al. [5] where a randomized, open-label, 4-phase cross-over pilot study was conducted to explore pharmacokinetics and pharmacodynamics of nebulized inhalation epinephrine. Eight young healthy men and women received the following 4 treatments: intramuscular epinephrine administration (0.3 mg), two different scheduled inhalation doses of 1 and 2 mL of a 4 mg/mL solution, equivalent to 4 and 8 mg, respectively and placebo inhalation (2 mL NaCl-solution). One additional subject received only the high inhalation dose and dropped out thereafter. The effectively delivered mean ( $\pm$ standard deviation) doses differed from the scheduled doses and were  $5.66 \pm 0.30$  mg over a mean duration of inhalation of  $18 \pm 5.90$  min and  $8.82 \pm 1.46$  mg over  $25.4 \pm 5.20$  min in the two inhalation treatment periods, respectively.

All inhalation treatments were administered using the Infectopharm Taschenvernebler® (Infectopharm Arzneimittel und Consilium GmbH, Heppenheim, Germany, identical to Omron Microair U22, Omron HealthcareEurope, Hoofddorp, Netherlands), set to the on–off modus for the inhalation–exhalation procedure. This membrane inhaler operates by nebulizing the full volume of the filled solution and is characterized by a volumetric median particle diameter of  $5.7 \pm 0.06$   $\mu$ m (Infectopharm Arzneimittel und Consilium GmbH, data on file).

### 2.2. Data preparation

For each period, PK measurements were scheduled at –15, –10, –5, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 20, 25, 30, 45, 60, 90, 120, 150, and 180 min relative to the administration. Explorative data analysis suggested high within-subject noise with arbitrary spikes distributed over the observed period (e.g. due to some external uncontrolled factors). To detect potential outliers that may interfere with model development, pooled data stratified by period were fitted by a local polynomial regression fit (LOESS) (with one degree) with automatic smoothing parameter selection via generalized cross-validation. Each observation which exceeded 50 ng/L (twice the lower limit of quantification of 25 ng/L) plus threefold the LOESS-predicted value was considered an outlier and excluded from further analysis. In total, 821 epinephrine measurements were available, of these 23 were excluded by the aforementioned method. Of the remaining 798 PK observations 272 (34%) measurements were below the lower limit of quantification (BQL) of 25 ng/L. To stabilize model development and to make the PK data more normal, a log transformation was applied to epinephrine plasma concentrations.

Heart rate as the observed PD parameter was scheduled at –15, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 15, 20, 25, 30, 45, 60, 90, 120, 150, and 180 min relative to administrations; additional measurements were done when considered informative on clinical grounds. Overall, 890 PD observations were available.

For the inhalation doses, the effectively inhaled amount corresponding to the effectively inhaled volume of epinephrine solution was used. This amount was calculated as the differences between weights of filled inhaler before and after inhalation, considering an

epinephrine concentration of 4 mg/mL in the inhaled solution with a specific weight of 1.00 g/mL.

### 2.3. Data analysis

The nonlinear mixed effects modeling approach was used for analysis. Parameters were estimated using the first-order conditional estimation method with interaction (FOCE-I + LAPLACE) implemented in the software package NONMEM® 7.3.0 (ICON Development Solutions, Ellicott City, MD, USA) [11]. Hereby, fixed effect parameters of the structural PK/PD model were estimated in log space. Due to the relatively high number of BQL PK observations (34%), the M3 method as suggested by Beal [12] was applied for handling BQL data. In this method, BQL observations are treated as censored (categorical data) and modeled simultaneously with the remaining continuous data; the likelihood for all the data is then maximized with respect to the model parameters. The likelihood for a BQL observation in particular is taken to be the likelihood that the observation is BQL under the model prediction [12,13].

The toolkit Perl-speaks-NONMEM [14] (version 4.2.0) and the graphical user interface Pirana [15] (version 2.9.0) were used as aids in model development and evaluation. R [16] (version 3.0.2.), the R-package Xpose4 [17] (version 4.4.0) and NPDE [18] (version 2.0) were used for data visualization, post-processing and evaluation of NONMEM outputs.

Model selection criteria were (i) the difference in objective function value ( $\Delta$ OFV) to discriminate between nested models ( $p \leq 0.05$ ), (ii) Akaike information criterion (AIC) for non-nested models, (iii) graphical diagnostic plots, (iv) precision of parameter estimates (covariance matrix inspection), (v) visual predictive check (VPC), and (vi) biological plausibility.

Confidence interval estimates were constructed using likelihood profiling [19].

### 2.4. Model development

The PK-PD model was built in a sequential manner. First, a PK model (see 3.1) for epinephrine plasma concentrations was developed, then a PD model (see 3.2) for the heart rate conditioned on the PK model parameter estimates using the PPP&D method (Population PK Parameters and Data) [20].

### 2.5. Model evaluation

A prediction-corrected VPC was performed to evaluate the predictive performance of the model [21,22]. Based on 10,000 simulations with the model, 95% nonparametric confidence intervals for the simulated data's 5th, 50<sup>th</sup>, and 95th percentiles for each bin across time were plotted and compared to corresponding percentiles of the observed data. For BQL observations and BQL predictions, a similar plot was created considering the corresponding proportion in the respective bins.

Normalized prediction distribution errors (NPDE) generated by 10,000 stochastic model simulations for each observation were used to evaluate whether the model adequately describes the observed data as classic methods based on residuals are not readily available for models accounting for BQL data [23]. The normalized prediction distribution errors (NPDE) should follow a standard normal distribution if the model correctly predicts the distribution from which the observations came [18]. Further, diagnostic graphs with NPDE plotted against the independent variable or the predicted dependent variable can help identify model misspecification [24]. The imputation method for BQL data as recently suggested by Nguyen et al. [23] was applied.

## 2.6. Monte Carlo simulation

The final model was used to assess the impact of the estimated interindividual variability on the PK and PD profiles through a Monte Carlo simulation using R [16] (version 3.0.2.). 10,000 individuals with different inhalation rates (sampled from the observed variability), weights, inhalation bioavailabilities, intramuscular absorption rates and pharmacodynamic parameters were sampled. All individuals received 0.3 mg intramuscular and an AUC<sub>0-inf</sub> (area under the plasma-concentration curve from time zero to infinity) equivalent inhalation dose (see Results).

## 3. Results

A schematic representation of the final model is provided in Fig. 1.

### 3.1. Pharmacokinetic model

#### 3.1.1. Distribution

Empirical one- and two-compartment models were tested. A two-compartment model was not superior to a one-compartment model, hence a simple one-compartment was chosen.

#### 3.1.2. Elimination

Epinephrine elimination was assumed to occur only from one pathway from the single systemic compartment. Linear (constant clearance) and non-linear (concentration-dependent clearance) elimination models were tested. Among the non-linear models, both saturable Michaelis–Menten kinetics, and kinetics where epinephrine accelerates its own metabolic clearance as previously described [25] were tested, but gave no conclusive results. Hence, a first-order process with an elimination rate constant (parameterized as the ratio of systemic clearance  $CL$  and systemic volume of distribution  $V$ ) finally described epinephrine elimination.

#### 3.1.3. Endogenous production

Endogenous production was assumed to follow constant zero-order kinetics where short-term peaks (e.g. due to psychic or physical arousals) were neglected. The endogenous self-infusion

rate  $R_0$  was fixed to a value of 0.01  $\mu\text{g}/\text{min}$  per kg bodyweight as reported by Cohen et al. [26].

#### 3.1.4. Intramuscular administration

Constant and time-varying first-order and zero-order absorption after instantaneous injection into a hypothetical intramuscular depot compartment were tested. A first-order absorption model ( $k_{a,i.m.}$ ) gave the best fit. It was tested whether the fraction absorbed  $F_{i.m.}$  into the systemic compartment (intramuscular bioavailability) was reduced; however, this parameter tended to be very close to unity during model development and was finally fixed at unity.

#### 3.1.5. Inhalation administration

A major simplification was that the inhaler released a constant epinephrine inhalation dosing rate  $k_0$  (as the ratio of inhaled dose and duration of inhalation) available for absorption. In physiology, this release is not constant due to differences during inhalation and exhalation and the corresponding on-off modus of the inhaler. But changes in concentration of epinephrine in the air flowing into the lung over time occur comparatively rapid and small and hence were not reflected by systemic epinephrine plasma concentrations. A hypothetical depot compartment representing the lung was incorporated. Drug was released from the inhaler with  $k_0$  into this lung compartment. From here, epinephrine could access the systemic compartment via first-order kinetics governed by the constant  $k_{a,inh.}$  but subject to a reduced inhalation bioavailability  $F_{inh.}$ . A model with direct infusion from the inhaler into the systemic compartment with  $k_0$  also subject to a reduced inhalation bioavailability  $F_{inh.}$  was also tested, but resulted to be slightly inferior. Mixed-order kinetics with a fraction subject to first-order absorption via the lung as a transit compartment and a second fraction acting as a direct infusion into the systemic compartment were not identifiable. The average observed  $k_0$  was 0.345 mg/min, while no significant difference between the two dosing treatments was obvious ( $p = 0.71$ ). Hence, we can assume a constant release rate  $k_0$  of 0.345 mg/min independent of the filling quantity of the inhaler, however, associated with moderate variability (coefficient of variation 18.4%), probably mainly due to different inhalation behavior among the subjects between the treatments within one subject. Hence, the amount of epinephrine inhaled depends mainly on the duration of inhalation  $T$ . Further, no evidence of time-dependent inhalation bioavailability  $F_{inh.}$  was found in this analysis.

### 3.2. Pharmacodynamic model

Linear, log-linear, and  $E_{\max}$  models implemented as direct effect models or with an hypothetical effect compartment (to introduce a lag time between plasma concentration and PD effect) having either an additive or proportional effect relative to the baseline were tested to describe the pharmacological effect of epinephrine on heart rate. As a simple link of only epinephrine plasma concentration to heart rate gave no good fit, two further parameters were introduced. First, the more pronounced rise in heart rate for the administration via inhalation suggested that concentration in venous blood samples may not be able to fully reflect changes in plasma concentrations; hence, the amount in the empirical lung compartment was used to serve as an approximation or surrogate for local concentrations in the lung and in the heart, and then as an additional driver for heart rate increase. Second, it was observed that the use of the inhaler per se (also in the placebo treatment) led to an elevation of baseline heart rate. As a more physiologically-based  $E_{\max}$  model was not identifiable, the following proportional log-linear model for the heart rate  $E$  was implemented of the form:

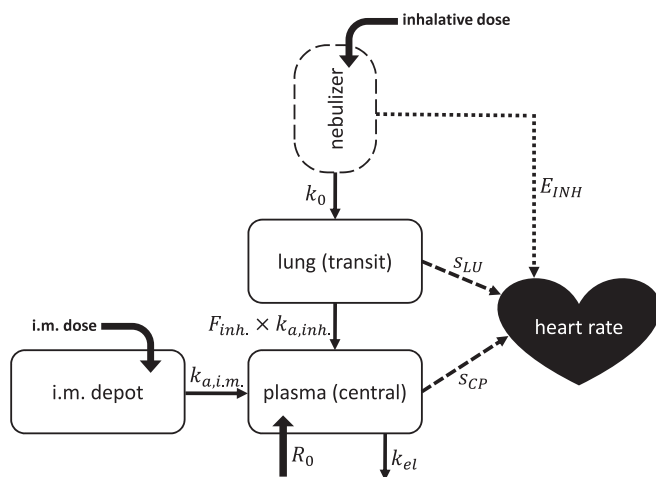


**Fig. 1.** Schematic illustration of the PK/PD-model. *i.m.* intramuscular,  $k_{el}$  elimination rate constant,  $R_0$  endogenous production rate,  $k_0$  inhalation dosing rate,  $F_{inh.}$  inhalation bioavailability,  $k_{a,inh.}$  inhalation absorption rate constant,  $k_{a,i.m.}$  intramuscular absorption rate constant,  $E_{INH}$  percentage baseline elevation during use of the inhaler,  $s_{CP}$  slope parameter linking plasma concentration to heart rate,  $s_{LU}$  slope parameter linking amount in lung to heart rate.

$$E = E_0 \times \left( 1 + s_{CP} \times \log \left( \frac{\hat{C}_{CP}(t)}{\hat{C}_{CP,SS}} \right) + E_{INH} \times I_{inh.} + s_{LU} \times \log \left( \hat{A}_{LU}(t) + 1 \right) \right) \quad (1)$$

where  $E_0$  is the baseline heart rate at the model-predicted baseline steady-state concentration of epinephrine  $\hat{C}_{CP,SS}$ ,  $s_{LU}$  is a slope parameter for the model-predicted epinephrine amount in the lung  $\hat{A}_{LU}(t)$ ,  $E_{INH}$  is the percentage by which the baseline heart rate is elevated during inhalation with the inhaler (e.g. due to exercise) and  $I_{inh.}$  takes the value 1 during inhalation and 0 else.

### 3.3. Random effect model

#### 3.3.1. Interindividual and interoccasional variability

Interindividual variability was tested for all model parameters in step-wise approach. The estimation of a full variance-covariance matrix was not feasible due to severe overparameterization and convergence problems given the small number of subjects. Different distributions in shape for interindividual variability were explored for the individual model parameters by testing transformations (log, Manly [27] and logit [28]) of random effects if the empirical Bayes estimates during model development indicated their use.

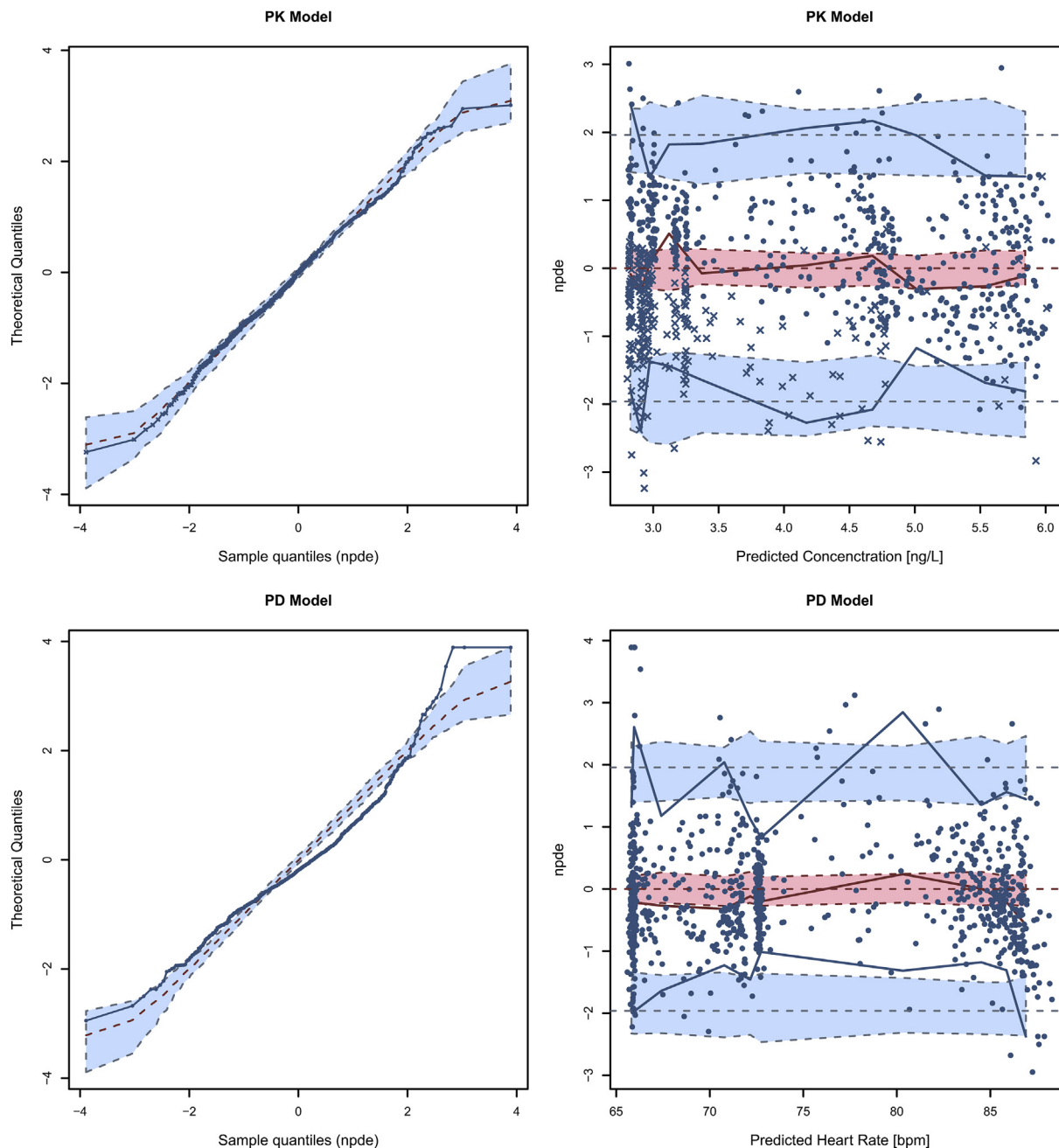


**Fig. 2.** NPDE diagnostic plots for the pharmacokinetic (PK) and pharmacodynamic (PD) model. Left panels: Quantile-quantile-plot (QQ-plot) of the distribution of the npde against the theoretical standard normal distribution. Right panels: Scatterplot of the npde versus the population predicted values. Dots represent npde from originally continuous data and crosses from imputed BQL data. Shaded areas represent 95% prediction intervals built on the distribution of npde using the simulations under the model. For the scatterplots, prediction intervals are constructed around the median, the 2.5th and 97.5th percentile; solid lines represent the median of the npde in the equally sized bins; horizontal dashed lines at  $\pm 1.96$  indicate the interval in which we expect 95% of the npde to be, and the line in the middle indicates  $y = 0$ .

In the PK model, interindividual and interoccasional variability was finally included for  $F_{inh}$ , using the Manly transformation due to skewed empirical bayes estimates:

$$\eta_{F_{inh},i}^T = \frac{\exp\left(\lambda_{F_{inh}} \left(\eta_{F_{inh},i} + TRT4 \eta_{F_{inh},i}^{Trt4} + TRT8 \eta_{F_{inh},i}^{Trt8}\right)\right) - 1}{\lambda_{F_{inh}}} \quad (2)$$

where  $\eta_{F_{inh},i}^T$  is the transformed random effect for individual  $i$ ,  $\lambda_{F_{inh}}$  is a shape parameter to modulate the skewness,  $\eta_{F_{inh},i}$  is a random effect of individual  $i$ ,  $TRT4$  and  $TRT8$  are indicator variables taking the value 1 in the respective treatment (4- or 8-mg-treatment) and 0 else, and  $\eta_{F_{inh},i}^{Trt4}$  and  $\eta_{F_{inh},i}^{Trt8}$  are corresponding random effects. As  $F_{inh}$  naturally lies between 0 and 1, a logit transformation for the individual parameter estimate was also applied:

$$F_{inh,i} = \frac{1}{1 + \exp\left(-\left(\log\left(\frac{F_{inh,pop}}{1 - F_{inh,pop}}\right) + \eta_{F_{inh},i}^T\right)\right)} \quad (3)$$

where  $F_{inh,pop}$  is the population estimate representing the median, and  $\eta_{F_{inh},i}^T$  as explained above. Hence, interoccasional variability was modeled as random intertreatment variability (4-mg-treatment as occasion 1, 8-mg-treatment as occasion 2) assuming that there is variability in the inhalation bioavailability independent of the dose. High variability was also observed in the intramuscular treatment and implemented for the distribution of the individual absorption rates  $k_{a,i,m,i}$  by the Manly transformation:

$$k_{a,i,m,i} = k_{a,i,m,pop} \exp\left(\frac{\exp\left(\lambda_{k_{a,i,m}} \eta_{k_{a,i,m},i}\right) - 1}{\lambda_{k_{a,i,m}}}\right) \quad (4)$$

Notably, this was significantly superior compared to the incorporation of interindividual variability on intramuscular bioavailability which tended to be unity (see above).

In the PD model, interindividual variability was estimated for the individual baseline heart rate  $E_{0,i}$  in terms of a classic

exponential model according to equation (5), as well as for the for the individual slope parameters  $SC_{P,i}$  and baseline increases  $E_{TV,i}$  through inhalation in the same manner.

$$E_{0,i} = E_{0,pop} \exp(\eta_{E_{0,i}}) \quad (5)$$

### 3.3.2. Residual variability

Since we decided to model the suddenly occurring peaks in all treatments as errors, the following model providing the greatest magnitude of residual variability for low concentrations compared to higher ones (in log space) was implemented gave the best fit:

$$\sigma_{PK,ij} = \sqrt{\left(\sigma_{PK,1} \left(1 - \frac{\hat{C}_{CP,ij}}{\xi + \hat{C}_{CP,ij}}\right)\right)^2 + \sigma_{PK,2}^2} \quad (6)$$

where  $\sigma_{PK,ij}$  is the standard deviation of the corresponding log-transformed concentration in the  $i$ th individual at time  $j$ ,  $\sigma_{PK,1}$  and  $\sigma_{PK,2}$  are residual standard deviation terms,  $\xi$  is a constant modulating  $\sigma_{PK,1}$ , and  $\hat{C}_{CP,ij}$  is the corresponding model prediction. But, as  $\sigma_{PK,2}^2$  tended to be zero as it was not identifiable, the final residual error model simplified to:

$$\sigma_{PK,ij} = \sigma_{PK,1} \left(1 - \frac{\hat{C}_{CP,ij}}{\xi + \hat{C}_{CP,ij}}\right) \quad (7)$$

A simple additive error model ( $\sigma_{PD,ij} = \sigma_{PD}$  for all  $i$  and  $j$ ) was used to describe residual variability in the PD model.

### 3.4. Model evaluation and parameter estimates

Diagnostic graphs using the NPDE are illustrated for the PK and PD models in Fig. 2. For the PK data the distributional quantile–quantile plot shows a very good match between theoretical and observed distribution of the npde, and no trend can be seen in the scatterplot of npde versus predicted concentrations. For the PD data

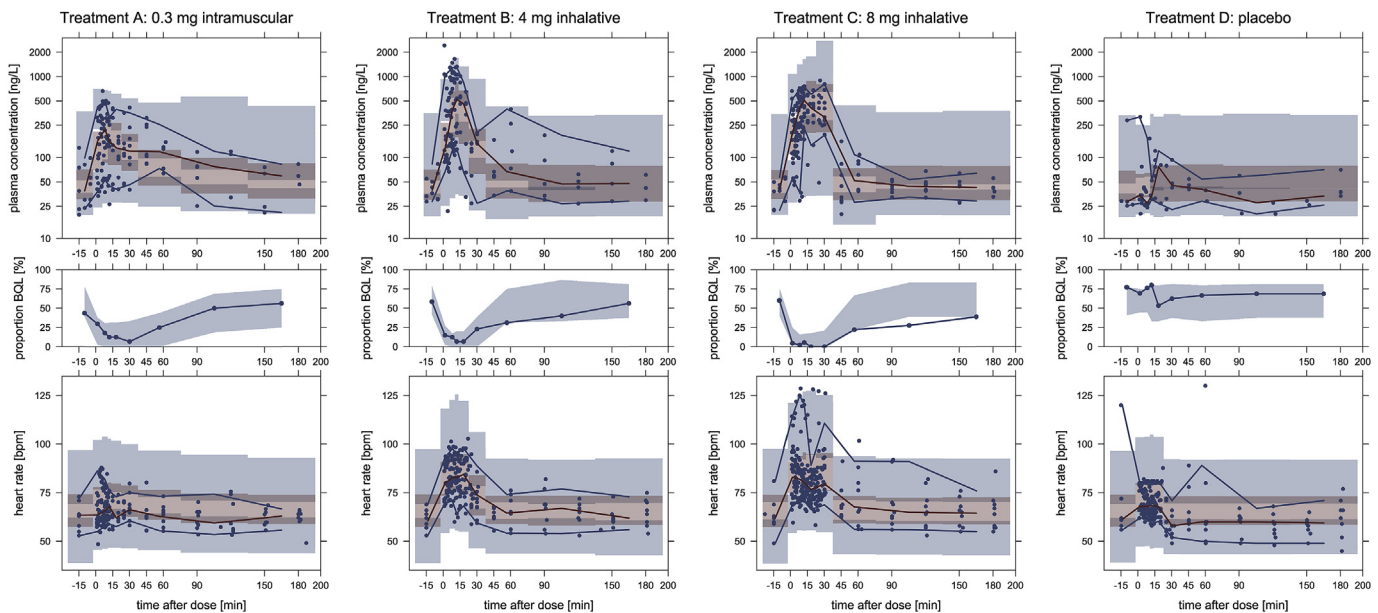


**Fig. 3.** Prediction-corrected visual predictive check showing the time courses of the observed and simulated data for each treatment. Concentration and heart rate panels: dots indicate prediction-corrected observations, solid lines indicate 5th, median and 95th percentile of observed data, shaded areas indicate a 95% confidence interval about the simulated median, the 5th and the 95th percentile of the simulated data. BQL panels: dots and lines indicate proportion of observed BQLs (data below quantification limit), shaded area indicate 90% confidence interval for the simulated proportion of BQLs. Censoring is performed before prediction correction, hence, it could happen that some values which are originally above the lower limit of quantification appear to be below after the correction.

the quantile–quantile plot of the npde shows slight right-skewness indicating that the model overpredicts heart rate slightly. No concerning trend is obvious in the scatterplot.

Fig. 3 shows the prediction-corrected VPC for the PK/PD model. While the overall trend of the PK data is well captured, there is some overpredicted variability mainly due to the high residual variance. The overall proportion of BQL is well predicted by the model. Concerning the PD model, the trend except a slight overprediction for the intramuscular and placebo treatment is well reflected while variability appears to be inflated to some extent.

Parameter estimates and respective confidence intervals are listed in Table 1. A sensitivity-analysis was performed by including all previously excluded observations (see Section 2.2) and rerunning the final model. Except for the residual variance component, no significant changes were observed in the final parameter estimates. Precision for the variance estimates of the interindividual variability parameters is low given the low number of subjects. Based on the model estimates, an epinephrine elimination half-life of 4.1 min could be determined. Inhaled epinephrine was available almost immediately and much more rapidly than via the intramuscular route for which an absorption half-life of 29 min was estimated. High interindividual and interoccasional variability was estimated for the inhalation bioavailability. Interoccasional variability appeared to be even more pronounced (Table 1). Median, 5% and 95% quantile estimates of the right-skewed distribution represent 4.7%, 0.26% and 14%, respectively.

An intramuscular dose of 0.3 mg yields a model-predicted expected baseline-corrected  $AUC_{0-\infty}$  of 140 ng min/L. Assuming this value as a gold standard, a duration of inhalation of approximate 18 min (corresponding to 6.3 mg) would yield an equivalent  $AUC_{0-\infty}$  for the inhalation route. Note that expected maximum concentration  $C_{max}$  values differ substantially. For a 70 kg person, the typical model-predicted  $C_{max}$  for inhaled epinephrine after approximately 18 min of inhalation would be 452 ng/L compared to 163 ng/L with intramuscular administration occurring approximately 14 min. However, this is reflected only by a moderate pharmacodynamic effect of an expected heart rate at  $C_{max}$  of 85 beats per minute (bpm) compared to 72 bpm.

For the average inhalation rate of 0.375 mg/L, the model-predicted expected steady-state concentration for a persistent inhalation (e.g. continuing until the doctor arrives with an “infinite” dose) would be 477 ng/L for a 70 kg person. This is still associated with only a moderate pharmacodynamic effect in heart rate (increase of 31% bpm).

Fig. 4 shows the typical time-course of epinephrine plasma concentrations for different duration of inhalations with the expected pharmacodynamic effect. Additionally, assuming a linear relationship between the concentration of the epinephrine solution in the inhaler and dosing rate, the model was applied to extrapolate the profile for a standard epinephrine solution of 1 mg/mL. For an equivalent  $AUC_{0-\infty}$ , a fictitious duration of inhalation of 73 min would be necessary, while plasma concentrations in the first crucial 30 min would be lower than for the intramuscular reference. The results of the Monte Carlo simulation to investigate the effect of interindividual variability for the above-mentioned target-dose to reach equivalent  $AUC_{0-\infty}$  on the PK and PD profile are illustrated in Fig. 5. The variability for inhaled epinephrine is obviously greater than for the intramuscular route, but no inferiority or safety concerns for the inhalation route become evident.

#### 4. Discussion

To our knowledge, this is the first population model describing the pharmacokinetics of inhaled epinephrine based on human data. An empirical pharmacokinetic-pharmacodynamic model linking

epinephrine pharmacokinetics after the intramuscular and inhalation route of administration to heart rate was developed. The model captures the overall trend well, and is considered to be useful for extrapolating the typical time-courses of the PK/PD profiles after inhalation epinephrine application for different dosing regimens in comparison to the intramuscular standard. The overall variability (as a composition of interindividual and intra-individual random effects) in plasma concentration profiles and respective pharmacodynamic response is also sufficiently captured given the small number of subjects.

A previously published comparison of different routes of administration in an animal model for rabbits concluded that neither the rate nor the extent of absorption was satisfactory after administration by inhalation [29]. Similarly, a recent review on epinephrine inhalers in emergency sets of patients with anaphylaxis claims that effective plasma concentrations cannot be reached with epinephrine inhalation [30]. However, a model-based quantification has been lacking. The findings of our analysis now are in contrast to these previous statements as they indicate that the combination of a highly concentrated epinephrine solution (4 mg/mL) with a mobile pocket inhaler as an effective treatment option

**Table 1**

Parameter estimates of the final PK/PD model. CI confidence interval, CV% coefficient of variation for the respective individual parameter in the population based on the final model, CL epinephrine plasma clearance, V volume of distribution,  $R_0$  endogenous production rate,  $F_{inh}$  inhalation bioavailability,  $k_{a,inh}$  inhalation absorption rate constant,  $F_{i,m}$  intramuscular bioavailability,  $k_{a,i,m}$  intramuscular absorption rate constant,  $E_0$  baseline heart rate,  $E_{INH}$  percentage baseline elevation during use of the inhaler,  $s_{CP}$  slope parameter linking plasma concentration to heart rate,  $s_{LU}$  slope linking amount in lung to heart rate,  $\omega^2$  variance estimate for variability in the respective parameter,  $\lambda$  shape parameters modulating the skewness of the respective distribution, TRT interoccasional variability between treatment periods,  $\sigma_{PK,1}$  standard deviation term for residual variability in concentration,  $\xi$  constant modulating  $\sigma_{PK,1}$ ,  $\sigma_{PD}$  standard deviation of residual variability in heart rate).

| Parameter                                      | Estimate | 95% CI <sup>a</sup> |
|------------------------------------------------|----------|---------------------|
| <b>Pharmacokinetic parameters [unit]</b>       |          |                     |
| CL [l/h]                                       | 2140     | 1940–2390           |
| V [l]                                          | 212      | 166–264             |
| $R_0$ [ $\mu$ g/min/kg]                        | 0.01     | Fixed               |
| $F_{inh}$ [%]                                  | 4.74     | 2.10–8.44           |
| $k_{a,inh}$ [ $h^{-1}$ ]                       | 59.3     | 37.4–110            |
| $F_{i,m}$ [%]                                  | 100      | fixed               |
| $k_{a,i,m}$ [ $h^{-1}$ ]                       | 1.42     | 0.189–3.78          |
| <b>Pharmacodynamic parameters [unit]</b>       |          |                     |
| $E_0$ [bpm]                                    | 65.1     | 59.4–71.4           |
| $E_{INH}$ [%]                                  | 9.68     | 6.16–13.3           |
| $s_{LU}$ [%/log(mg)]                           | 22.9     | 12.0–33.6           |
| $s_{CP}$ [%/log(ng/l)]                         | 4.54     | 3.05–6.06           |
| <b>Interindividual/-occasional variability</b> |          |                     |
| $\omega_{F_{inh}}^2$                           | 0.509    | 79 <sup>b</sup>     |
| $\omega_{F_{i,m}}^2$                           | 0.718    | 0.235–3.13          |
| $\omega_{k_{a,inh}}^2$                         | –0.482   | –1.04 to –0.117     |
| $\omega_{k_{a,i,m}}^2$                         | 2.45     | 0.381–33.9          |
| $\lambda_{k_{a,i,m}}$                          | –0.589   | –2.98 to –0.0347    |
| $\omega_{E_0}^2$                               | 0.0154   | 0.00663–0.0469      |
| $\omega_{E_{INH}}^2$                           | 0.123    | 0.0184–0.622        |
| $\omega_{s_{CP}}^2$                            | 0.108    | 0.00947–0.509       |
| <b>Residual variability</b>                    |          |                     |
| $\sigma_{PK,1}$                                | 1.09     | 0.967–1.23          |
| $\xi$ [ng/L]                                   | 176      | 134–236             |
| $\sigma_{PD}$ [bpm]                            | 6.66     | 6.35–6.98           |

<sup>a</sup> Based on likelihood profiling.

<sup>b</sup> Coefficient of variation for the corresponding parameter in the population derived from Monte Carlo simulations of the estimated transformed distribution based on normally distributed untransformed random effects.

<sup>c</sup> Coefficient of variation for the corresponding parameter based on log-normal distribution:  $\sqrt{\exp(\omega^2) - 1}$ .

from a pharmacokinetic and pharmacodynamic point of view (Fig. 4).

The duration of inhalation can be varied to obtain the desired exposure in terms of AUC. Besides overall exposure, a rapid provision of epinephrine is considered to be important for the effective treatment of anaphylaxis. The model demonstrates that epinephrine plasma concentration increases even more rapidly after inhalation compared to i.m. administration, while only a moderate additional effect on heart rate is to be expected (Fig. 4). Accordingly, the results of the model support the previously published results of Breuer et al. [5] that inhaled epinephrine does not generate a safety concern compared to the conventional intramuscular route of administration when looking solely at heart rate. Additionally to the fact that the absorption is more rapid, it may be postulated that the locally high concentrations in the lung and afferent veins to the heart might be advantageous to resolve bronchoconstriction [7]. Furthermore, the model shows that venous plasma concentrations do not fully reflect the local concentrations in the heart. These drive additionally the pharmacodynamic effect since the inclusion of a hypothetical transit compartment (representing the lung) and linking the amount in this compartment also to pharmacodynamic effects as a surrogate for local heart concentrations significantly

improved the fit. These potentially locally higher concentrations might also be seen as an advantage to support essential hemodynamic stabilization in anaphylaxis.

The point estimates of the variance components expressing interindividual and interoccasional variability are very high. Given the number of subjects, it is clear that we cannot fully trust them from a quantitative point of view. But from a qualitative point of view, the results of the model development identified inhalation bioavailability and the intramuscular absorption rate constant as major determining sources of variability between subjects (and periods), rather than interindividual variability in clearance or volume of distribution. Interoccasional variability appeared to be even greater than between-subject variability for inhalation bioavailability. According to our observations during conductance of the trial, we speculate that this interoccasional variability might arise from variability in the volunteers' inhalation technique. The impact of this variability has been assessed in a Monte Carlo simulation (Fig. 5). As indicated by the prediction bands, the results show that inhaled epinephrine is not inferior to intramuscular administration without safety concerns. Additionally as in the case of intramuscular autoinjection as well [31], this shows the importance of intensive training with the inhaler and education about

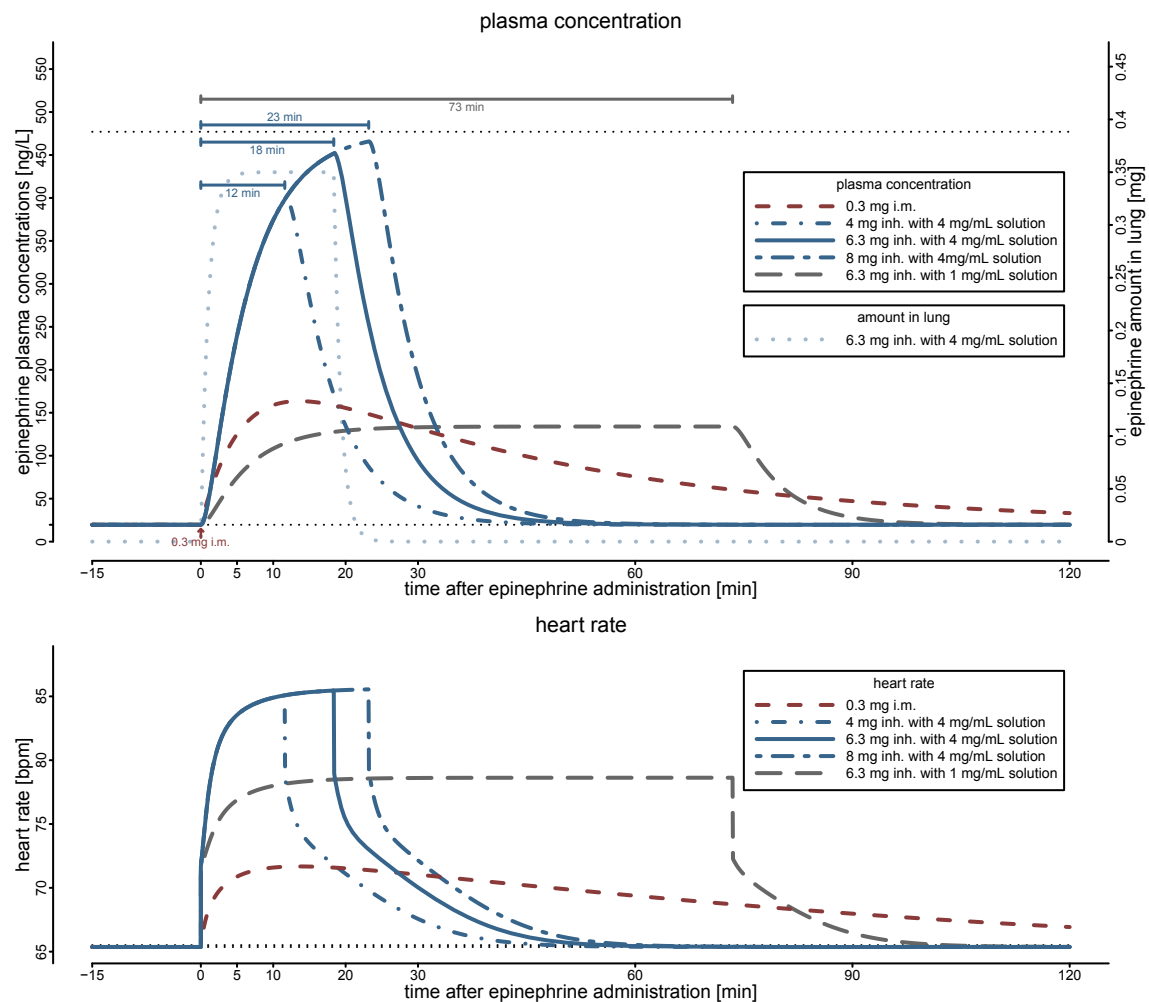


**Fig. 4.** Model-predicted typical epinephrine plasma concentrations (upper left axis), amount of epinephrine in the hypothetical lung compartment (upper right axis), and expected effect on heart rate (lower panel) based on different inhalation (inh.) durations compared to intramuscular (i.m.) application. The two horizontal small dotted lines indicate the model-predicted steady state (lower line) at baseline and at an inhalation rate of 0.375 mg/min (upper line). Other lines as indicated by the legend. For the inhalation route, three different inhalation durations are shown with an epinephrine concentration of 4 mg/mL in the solution for the inhaler and one scenario is shown with an epinephrine concentration of 1 mg/mL in the solution. The amount of epinephrine in the lung is just shown for the theoretical inhalation overall dose of 6.3 mg with a 4 mg/mL solution in the inhaler.

anaphylaxis to minimize treatment failure due to a lack of absorption of epinephrine by means of device misuse.

From an efficacy perspective, however, the virtually immediate absorption (Table 1) of inhaled epinephrine and the apparently very short depot effect in the lung (Fig. 4) indicate that therapeutic effects such as protection against allergic reactions may not last much longer than the inhalation itself. Hence, it might be advisable to use larger fill volumes (at least 2 mL equivalent to 8 mg) to warrant a sufficient duration of inhalation or repeated dosing. From a safety perspective on the other hand, this means that in the case of adverse events any further systemic exposure can be stopped immediately.

It needs to be emphasized that the use of a high epinephrine concentration (e.g. 4 mg/mL) in the inhaler seems to be essential. The application of the standard solution of 1 mg/mL (used for example for intravenous purposes) may not provide sufficient systemic exposure (Fig. 4).

Despite these promising features of the model, several limitations need to be considered. A major weakness of the model is the relatively high degree of uncertainty in the parameter estimates and the corresponding simulations. This is naturally typical in population-based approaches with only a small number of subjects,

but is certainly also due to the considerably high variability, and may also be a sign for some model misspecification. One should note, however, that the apparent overpredicted variability in the 8-mg-treatment (Fig. 3) is qualified to some extent by having a closer look at the data: in the 4-mg-treatment, there are more relatively high observations between 500 and 1500 ng/L compared to the 8-mg-treatment which can only be explained – to the best of our knowledge after model development – by random. In the presented analysis, we finally accepted a moderate degree of over-parameterization from a pure statistical point of view in favor of estimating the desired parameters, such as the variability in the inhalation bioavailability. Further, one needs to take account of slight model misspecifications (Figs. 2 and 3) and be cautious when looking at the predicted PK/PD links. First, the model does not account for rapid physiologic inclines in endogenous epinephrine releases (the model assumes a constant baseline release of endogenous epinephrine); second, relatively high residual unexplained variability needs to be considered. In summary, the “true”  $C_{max}$  and correspondingly the expected pharmacodynamic effect on heart rate might be substantially higher. Note that even the highest concentrations were removed from this analysis *a priori*, as we do not have a plausible explanation for such rapid increases and

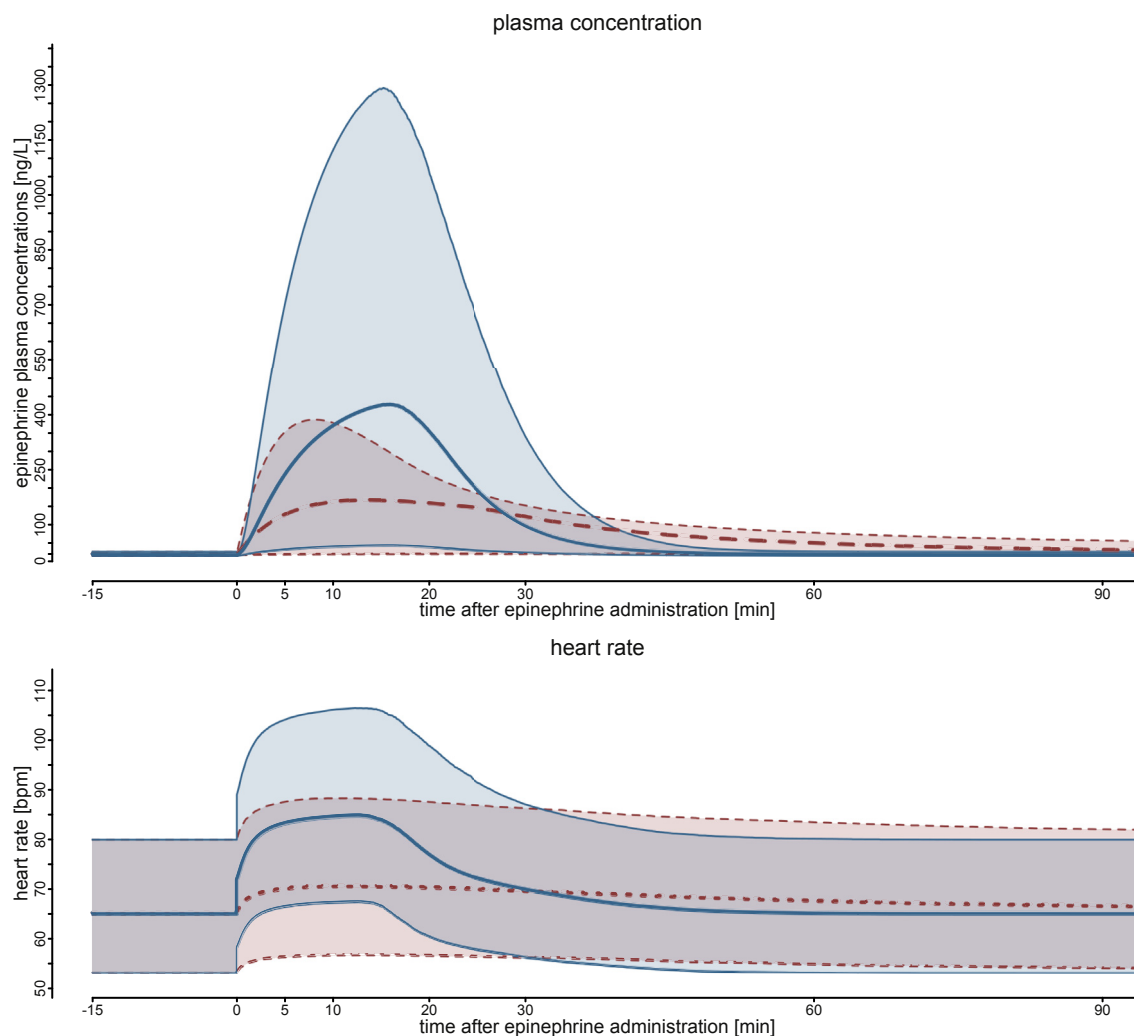


**Fig. 5.** Monte Carlo study on epinephrine plasma concentrations (upper panel) and expected heart rate (lower panel) to investigate the effect of variability for the inhalation (solid lines) and intramuscular (dashed lines) route of administration. 10,000 simulations were ran with an inhalation dose of 6.3 mg (average inhalation duration of around 18 min) and an intramuscular dose of 0.3 mg. For a typical individual in the population, these doses are  $AUC_{0-inf}$  equivalent. Solid lines indicate the median, shaded areas and dashed lines represent the 90% prediction interval.

equally rapid decreases (increase of up to 2000 ng/L within 1 min and normalization to baseline in the next minute). However, these spikes occurred independently of the route of administration and also in the placebo phase. Therefore, we do not consider that conclusions concerning the route of administrations are strongly confounded. Another limitation is that the endogenous production rate needed to be fixed, and hence all other parameters (in particular clearance and volume of distribution) may be mis-scaled. However, this is not to be expected to have impact on the conclusions and implications of the results. Notably, the parameters characterizing the absorption for the inhalation route ( $k_{a,inh}$  and  $F_{inh}$ ) represent empirical hybrid parameter; they are affected by metabolism in the lung, exhalation of epinephrine, potential misuse of the inhaler, and finally technical characteristics of the inhaler such as the delivered dose and the fine particle fraction able to reach the lung.

Finally, we need to point out that this study was conducted in healthy adult volunteers. Applicability of the results of this analysis to patients or even pediatric patients is unclear. Patients may suffer for example from bronchial or tracheal contraction and may have problems to inhale efficiently. On the other hand, inhalation right in the beginning of an imminent contraction might be a powerful treatment due to the local exposure. In pediatrics, a different physiology per se might need to be considered additionally. Hence, only dedicated clinical trials could further assess the efficacy of inhaled epinephrine in the clinical setting.

## 5. Conclusion

The proposed model suggests that the use of epinephrine via inhalation may offer an attractive self-treatment option in patients with imminent anaphylaxis who are reluctant to make an intramuscular injection. A duration of inhalation about 15–20 min (equivalent to approximately 5–7 mg epinephrine) seems to be appropriate in a typical (healthy) adult patient to mimic the exposure of 0.3 mg i.m. administered epinephrine. High interindividual and interoccasional variability in the inhalation bioavailability (probably mainly reflecting the inhalation technique) needs to be considered. The model indicates that inhaled epinephrine is provided almost immediately after the start of inhalation and will disappear rapidly after stopping inhalation. Finally, expected  $C_{max}$  values are substantially higher for inhaled epinephrine, however, this is associated only with moderate elevated hemodynamic effects and indicates that additional safety concerns might not to be expected. If inhaled epinephrine is not sufficiently effective, intramuscular epinephrine may be added at any time. Note that both the suggested dosing as well as the conclusions need to be treated with caution as there is a high degree of uncertainty in all model parameter estimates given the low number of only 9 subjects. Furthermore, parameters (e.g. inhalation bioavailability) might substantially differ in patients. Hence, clinical efficacy and safety in patients and in particular in children needs to be assessed in larger trials in patients.

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