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

Sebastian Frechen [a, *], Ahmed Abbas Suleiman [a], Ali Mohammad Nejad Sigaroudi [a], Bertil Wachall [b], Uwe Fuhr [a]

[a] Department of Pharmacology, Clinical Pharmacology, Cologne University Hospital, Cologne, Germany
[b] INFECTOPHARM Arzneimittel und Consilium GmbH, Von-Humboldt-Str.1, 64646 Heppenheim, Germany

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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-live 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.

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 L-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

* Corresponding author.
E-mail address: sebastian.frechen@uk-koeln.de (S. Frechen).

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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 (±standard deviation) doses differed from the scheduled doses and were 5.66 ± 0.30 mg over a mean duration of inhalation of 18 ± 5.90 min and 8.82 ± 1.46 mg over 25.4 ± 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 ± 0.06 μm (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 (ΔOFV) 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, 50th, 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.