PHARMACOKINETICS AND DISPOSITION

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Pharmacokinetic–pharmacodynamic model for the anticholinergic effect of glycopyrrolate

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Abstract Objective. The purpose of this study was to develop and test a pharmacokinetic–pharmacodynamic (PK–PD) model for the anticholinergic effect of glycopyrrolate in eight healthy male volunteers.

Methods: First, arterial drug concentration (Cₚ) data after a single intravenous (i.v.) bolus injection (5 µg/kg) were individually fitted to a three-compartment PK model. Second, the effect of a 2-h glycopyrrolate i.v. infusion (5 µg/kg/h) on the mean R–R interval (RRI) and the Hayano index of the high frequency variability of RRI (HF CCV) was modelled using an effect-compartment, inhibitory sigmoidal Eₘₐₓ model, with the individual PK parameters from the first part as constants. Third, the developed model was tested using a computer-driven infusion which aimed at two ascending steady-state effect-site concentrations (Cₑ) at 1-h intervals, corresponding to 20% and 80% of the maximal effect (Eₘₐₓ) observed in the second part.

Results: Modelling of the HF CCV data yielded the following mean (± SD) estimates: concentration at 50% of Eₘₐₓ (EC₅₀), 2.46 ± 0.58 ng/ml, equilibration half-time (t₁/₂ kₑ₀), 42.5 ± 7.7 min, and sigmoidicity factor (γ), 7.26 ± 2.82. The corresponding values for RRI data were 2.79 ± 0.52 ng/ml, 58.3 ± 17.2 min, and 4.75 ± 1.56. During the computer-controlled two-step infusion (performed using HF CCV as the effect variable), the measured Cₚ approached the targeted Cₑ in most of the subjects, while the observed effect appeared to surpass the targeted levels.

Conclusion: Although we were able to develop individual PK–PD models for glycopyrrolate, maintaining a stable anticholinergic effect in the computer-driven infusion appeared to be difficult. This is probably due to intra-individual variability in the PK–PD parameters and the extremely steep concentration–effect relationship of glycopyrrolate.

Keywords Glycopyrrolate · Heart rate · Pharmacokinetic–pharmacodynamic modelling

Introduction

Spectral analysis of heart rate variability is a powerful non-invasive method of quantifying drug effects on autonomic nervous system activity. The high frequency (HF) spectral component, which reflects respiratory sinus arrhythmia mediated by the vagus nerve, may provide a dynamic index of cardiac parasympathetic tone (Pomeranz et al. 1985). In our previous investigation, a single i.v. bolus dose (5 µg/kg) of glycopyrrolate, a commonly used parasympatholytic agent, induced profound vagolytic effects indicated by a diminished HF power (Scheinin et al. 1999). Pharmacokinetic–pharmacodynamic (PK–PD) modelling was found to be feasible with venous radioreceptor assay (RRA) concentration data (Kaila et al. 1990). The concentration–effect curve for glycopyrrolate was sigmoidal and there was a clear lag between plasma concentration and effect (hysteresis). The average equilibration half-time (t₁/₂ kₑ₀−ln(2)/kₑ₀) was 21 min (Scheinin et al. 1999).

In the present trial, the concentration–effect relationship of glycopyrrolate was further characterised by assessing the hysteresis both during increasing and decreasing drug concentrations in arterial blood. We also intended to validate the PK–PD link model and investigate whether stable anticholinergic effects could be maintained using the derived PK and PD parameters. During three different sessions, individual PK (part 1) and PD action (part 2) of glycopyrrolate were investigated in eight healthy volunteers, and then, effect compartment (link) PK–PD modelling was performed.
for each subject. The developed model was tested using a computer-driven infusion (part 3) which targeted first at 20% and then at 80% effect of the previously observed individual $E_{\text{max}}$, representing the ends of the log-linear part of the sigmoidal concentration–effect curve (Meibohm and Derendorf 1997).

### Methods

**Subjects and study design**

This open study with eight healthy male volunteers (age 24–29 years, weight 60–80 kg, height 168–191 cm) investigated the pharmacokinetics and pharmacodynamics of glycopyrrolate during three different sessions, with at least 7 days wash-out period between consecutive administrations. Medication and alcohol were forbidden during the study. Medication was continued, including insulin for 24 h prior to the sessions. The study protocol was approved by the ethics committee of Turku University Hospital. Written informed consent was obtained from each subject.

**Study procedure**

The study days always started between 0800 hours and 0900 hours. The subjects had fasted from midnight, they were in supine position during the sessions and a 30-min stabilisation period preceded the baseline measurements. An i.v. antecubital cannula was inserted for drug administration and continuous glucose infusion (100 ml/h of 5% dextrose; to prohibit hunger). An intra-arterial cannula was inserted in the other arm (a. radialis) for arterial blood sampling. Thereafter, the study days continued as follows:

**Part 1**

Glycopyrrolate (glycopyronium bromide, Gastrodyne, Leiras, Turku, Finland) was administered as a single i.v. bolus injection (5 µg/kg). For the determination of glycopyrrolate concentrations in plasma, arterial blood samples were drawn at baseline, at 10, 20, 30 and 45 s, at 1, 1.5, 2, 2.5, 3, 4, 5, 7.5, 10, 15, 20, 30 and 45 min, and at 1, 1.5, 2, 3, 4, 5, 6, 8 and 12 h.

**Part 2**

The subjects were connected to an electrocardiogram (ECG) transducer unit (M9407, Medikro, Finland) for repeated 5-min ECG recordings, during which they maintained a fixed breathing rate (15/min, i.e. 0.25 Hz). After baseline blood samples and ECG recordings, the subjects received a constant 2-h glycopyrrolate i.v. infusion (5 µg/kg/h) administered via an infusion pump (Braun Perfusor ED 2, B. Braun AG, Germany). The total dose of 10 µg/kg was supposed to induce supramaximal or near maximal muscarinic receptor blockade (Scheinin et al. 1999). Periodic 5 min ECG recordings were repeated with 10-min intervals during the infusion and a 3-h follow-up period, i.e. altogether for 5 h. Arterial blood samples for drug concentrations were drawn after each recording.

**Part 3**

After baseline measurements, glycopyrrolate was infused with a computer-controlled (STANPUMP) infusion pump (Harvard 22 Basic Syringe Pump, Harvard Apparatus, South Natick, Mass.) for 2 h, aiming at two ascending steady-state effect-site concentrations giving 20% (during the first hour) and 80% (during the second hour) of the maximal anticholinergic effect ($E_{\text{max}}$) observed in part 2. Individual PK and PD parameters obtained by modelling data from part 1 and part 2 were used to design the actual dosing scheme for each subject. During the infusion, ECG was registered four times within each 1-h step (5-min recordings, 10-min intervals). After the end of the infusion, ECG was recorded at the predicted time points of 50% and 20% of individual $E_{\text{max}}$, and at 1, 2 and 3 h. Blood samples were drawn at 15-min intervals during the infusion (i.e. after each recording), and at 30 s, 2 min, 5 min, 10 min, 30 min, 1 h, 2 h and 3 h after the end of the infusion.

**PK analysis**

The arterial blood samples (5 ml, drawn into plastic tubes containing K$_2$EDTA as an anticoagulant) were centrifuged, and the separated plasma was stored at −70°C until analysed. Glycopyrrolate concentrations were measured using the RRA method (Kaila et al. 1990). A linear three-compartment open model with bolus input was used for PK calculations (based on the drug concentration data collected in part 1). Nonlinear least squares fits of the data were performed using the computer program PCNONLIN 4.2 (Scientific Consulting Inc., Apex, N.C.; Scheinin et al. 1999). The following PK parameters were calculated: exponential rate constants for rapid distribution ($\lambda_1$), slow distribution ($\lambda_2$) and elimination ($\lambda_3$), the corresponding half-lives ($t_{1/2}$ = ln(2)/$\lambda_1$, $t_{1/2}$ = ln(2)/$\lambda_2$, $t_{1/2}$ = ln(2)/$\lambda_3$, etc.), volume of the central compartment ($V_c$), volume of distribution at steady state ($V_s$), total plasma clearance (CL) and area under the concentration–time curve (AUC). The respective microconstants, such as the rate constant for transfer from compartment 2 to 1 ($k_{21}$), were also computed.

**Pharmacodynamics: analysis of heart rate variability**

The ECG signal from the amplifier output was analogue-to-digital converted with a temporal resolution of 200 Hz (M9401 serial interface unit, Medikro, Finland), recorded and stationary time series of consecutive R–R intervals (RRIs) were generated. These beat-by-beat RRI time series were then subjected to power spectral analysis in frequency domain using modified covariance autoregressive modelling with fixed model order of 14, performed using a software package CAFTS (Medikro, Kuopio, Finland; Scheinin et al. 1999). Total power, i.e. the variance of RRI variability, was generated after linear detrending of the signals. The HF power of RRI variability was computed by integration over the frequency band from 0.15 Hz to 0.40 Hz, as previously recommended (Task force of the European Society of Cardiology 1996). The Hayano index (coefficient of component variance, CCV) for the HF spectral component was computed as follows (Hayano et al. 1991):

$$\text{HF CCV} = \sqrt{\frac{\text{HF power}}{\text{RRI}}} \cdot 100 \quad \text{(1)}$$


**PK–PD modelling**

As previously described in detail (Scheinin et al. 1999), effect compartment PK–PD modelling was performed using a sigmoid inhibitory $E_{\text{max}}$ model with baseline effect, in which the individual PK parameters from part 1 were used as constants (Colburn 1981; Holford and Sheiner 1981; Meibohm and Derendorf 1997). The investigated effect variables were the Hayano index (HF CCV) and the mean RRI. The equation for effect-site concentration ($C_e$) during and after the constant glycopyrrolate infusion in part 2 was: