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Original article

# Population pharmacokinetic modeling of furosemide in patients with hypertension and fluid overload conditions

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ABSTRACT

*Background:* Furosemide is a loop diuretic drug frequently indicated in hypertension and fluid overload conditions such as congestive heart failure and hepatic cirrhosis.
The purpose of the study was to establish a population pharmacokinetic model for furosemide in Indian hypertensive and fluid overload patients, and to evaluate effects of covariates on the volume of distribution (V/F) and oral clearance (CL/F) of furosemide.
*Methods:* A total of 188 furosemide plasma sample concentrations from 63 patients with hypertension or fluid overload conditions were collected in this study. The population pharmacokinetic model for furosemide was built using Phoenix NLME 1.3 software. The covariates included age, sex, body surface area, bodyweight, height and creatinine clearance (CRCL).
*Results:* The pharmacokinetic data of furosemide was adequately explained by a two-compartment linear pharmacokinetic model with first-order absorption and an absorption lag-time. The mean values of CL/F and Vd/F of furosemide in the patients were 15.054 $Lh^{-1}$ and 4.419 L, respectively. Analysis of covariates showed that CRCL was significantly influencing the clearance of furosemide.
*Conclusion:* The final population pharmacokinetic model was demonstrated to be appropriate and effective and it can be used to assess the pharmacokinetic parameters of furosemide in Indian patients with hypertension and fluid overload conditions.


## Introduction

Furosemide, a most commonly prescribed diuretic, is indicated in the treatment of hypertension and edema related with fluid overload conditions such as hepatic cirrhosis and congestive heart failure (CHF) [1–3]. It reversibly inhibit the $Na^+/K^+/2Cl^-$ carrier in the luminal membrane of the thick ascending limb by combining with its $Cl^-$ binding site [4]. The blood pressure-lowering effect of furosemide is mainly explained by a reduction in plasma volume [5]. Furosemide is absorbed from the gastrointestinal tract, and its peak effect occurs within 1 h after oral administration [6]. Furosemide strongly bound to plasma protein (91–99%), predominantly to anionic sites on albumin [7]. Approximately 60–70% of the furosemide dose is excreted unchanged in urine, and the remaining is glucuronidated [7,8]. The plasma half-life of furosemide is approximately 90 min (longer in renal failure).

Population pharmacokinetics is the study of sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest. The study of population pharmacokinetics represents an important aspect of drug development and plays a key role in finding the right dose. Population pharmacokinetic models are scientific and more efficient in describing the pharmacokinetic behavior of investigated drug and to evaluate the possible covariates that may influence pharmacokinetic intra and inter-variability [9,10]. Among plenty of furosemide pharmacokinetic studies, only a little number of them has used population pharmacokinetic approach [11–15], but these approaches have not been studied in Indian patients. The main aspect of present work is to develop a population pharmacokinetic model of furosemide and to identify the impacts of Indian patient characteristics on furosemide pharmacokinetic variability.

## Materials and methods

### *Subjects and study design*

Subjects at least 18 years of age and receiving oral furosemide for the treatment of hypertension or fluid overload conditions were

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recruited. No other eligibility criteria were intended to ensure a population representative of individuals receiving furosemide. Informed consent was obtained from all participants. Institutional Ethics Committee (IEC) approval was obtained before start of the study (Letter No: UCPSc/KU/BA/03/2013). The patients' demographic data were noted regarding age, gender, bodyweight, height, body surface area (BSA), creatinine clearance (CRCL) and concomitant medications taken along with furosemide.

Random sparse sampling design was used in the study. The dosage regimen of 40 mg once-daily was followed, which was fixed by the physician. Venous blood samples were drawn at 0.5, 1.0, 2.0, 3.0, 4.0, 6.0 and 8.0 h after the oral administration of furosemide. Blood samples were collected in lithium heparin vacutainer and centrifuged at 3000 × *g* for 8 min at room temperature. The samples were kept at −20 °C until further processing.

### *Bioanalytical assays*

The plasma concentrations of furosemide were quantified by a validated ultra-fast liquid chromatography coupled with photodiode array detection (UFLC-PDA; Shimadzu Corporation, Kyoto, Japan), using 276 nm, as preferred wavelength. The system consisted of binary LC-20AD pumps with a micro gradient mixer. A 250 mm × 4.6 mm, 5 μm RP C18 column (Phenomenex Luna) was used at 35.0 ± 2.0 °C. All of the operations and analysis of data obtained were controlled by lab solutions software. Liquid-phase extraction procedures were performed using methanol as an extracting solvent. A gradient program was employed using a mobile phase A of 0.1% triethylamine in water (pH 3.25) and an organic mobile phase B of methanol. The gradient was 5% B (0–2 min), 30% B (2.1–6.5 min) and 70% B (6.51–10 min). Mobile phases were duly degassed ultrasonically for 15 min. Efficient and symmetrical peaks were obtained at a flow rate of 0.8 mL/min. The retention time for furosemide was 3.8 min. The present method was validated for the estimation of furosemide in human plasma over the concentration range of 200–2200 ng/mL. The proposed method was fully validated by determining linearity, accuracy, precision, lower limit of quantification, recovery and stability.

### *Population pharmacokinetic modeling*

The population pharmacokinetic model for furosemide was developed using Phoenix NLME (version 1.3; Certara L.P., St. Louis, MO, USA). The first-order conditional estimation method with the η-ε interaction option (FOCE ELS) was used during pharmacokinetic model development. Initially, the basic structural model without covariates was examined. The best structural model was chosen based on assessment of the objective function value (OFV, equal to the twice the negative log likelihood [-2LL] value) and the visual inspection of diagnostic plots [16,17]. During the process of building a kinetic model, a constant coefficient of variation error model describes the inter-individual variability.

The inter-individual variability for fundamental pharmacokinetic parameters was modeled by the log normal distribution, as described in Eqs. (1) and (2):

$$CL/F_j = tvCL.\exp(\eta_{jCL/F}) \quad (1)$$

$$V/F_j = tvV.\exp(\eta_{jV/F}) \quad (2)$$

where $\eta_{jCL/F}$ is a random variable that denotes the difference between individual clearance of the *j*th individual ($CL/F_j$) and the population typical value (tvCL). The random variable $\eta_{jCL/F}$ is a normally distributed with an expectation of zero and a variance of $\omega^2_{CL/F}$.

**Table 1**
Demographics of the study patients.

| Charactaristic | Median | Range |
|---|---|---|
| Gender (M/F) | 39/24 | |
| Age (years) | 53 | 28–65 |
| Body weight (kg) | 67 | 51–77 |
| Height (cm) | 165 | 155–179 |
| BSA ($m^2$) | 1.77349 | 1.4961–1.95666 |
| CRCL (mL/min)[a] | 69.65 | 31.9–126.67 |
| Furosemide dosing regimen (mg/day) | 40 | |

[a] According to Cockcroft-Gault formulation, BSA Body Surface Area, CRCL Creatinine Clearance.

### *Population covariate analysis*

The influence of covariates such as age, body weight, gender, height, BSA and CRCL were evaluated. The possible covariates were explored using stepwise forward inclusion ($p \leq 0.05$) and stepwise backward deletion (a reduction in −2LL greater than 6.63, $p \leq 0.01$) [18]. Continuous covariates were examined using power equations, whereas categorical variables were included into the model as index variables.

### *Model validation*

The adequacy of the final model was simultaneously evaluated using bootstrapping and visual predictive check (VPC) method [19]. A bootstrap (n = 1000) was performed by resampling the subjects from the original data set. The final model parameter estimates obtained from the original dataset were compared with 95% confidence intervals (CIs) of the bootstrap estimates. A VPC was performed using 1000 dataset simulations. The 5th, 50th and 95th percentiles of the simulated concentrations were calculated and then checked by visual inspection to evaluate how the simulated results are related with the observed furosemide concentrations.

## Results

### *Subjects*

A total of 63 subjects with hypertension or fluid overload conditions were included in the dataset. Table 1 summarizes the key demographics of the patients. A total of 188 samples were collected in the study.

**Table 2**
Changes in −2LL with covariates.

| Covariates | −2LL |
|---|---|
| Base model | −103.608 |
| CRCL, Age on CL/F; CRCL, Age, BSA on V/F | −118.991 |
| CRCL, Age on CL/F; CRCL, Age on V/F | −115.123 |
| CRCL on CL/F; CRCL, Age on V/F | −133.104 |
| CRCL on CL/F; CRCL on V/F | −113.703 |
| CRCL, Age on CL/F; Age on $K_a$ | −146.471 |
| CRCL, Age, BSA on CL/F; CRCL on V/F; Age on $K_a$ | −116.194 |
| CRCL, Age on CL/F; CRCL, BSA on V/F; Age on $K_a$ | −131.137 |
| CRCL, Age, BSA on CL/F; CRCL, age, BSA on V/F; Age on $K_a$ | −122.87 |
| CRCL, Age, BSA on CL/F; Age on $K_a$ | −118.489 |
| CRCL, Age, BSA on CL/F; Age on V/F; Age on $K_a$ | −119.001 |
| CRCL, Age, BSA on CL/F; CRCL, age, BSA on V/F | −120.041 |
| CRCL, Age on CL/F; CRCL, age on V/F; Age on $K_a$ | −119.561 |

–2LL, twice the negative log likelihood; BSA, Body Surface Area; CRCL, Creatinine Clearance; Ka, first-order absorption rate constant; V/F, volume of distribution for the central compartment.