

# Population pharmacokinetic and pharmacodynamic modelling of the effects of nicorandil in the treatment of acute heart failure

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## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Nicorandil injection is used for unstable angina and for acute heart failure in Japan.
- The pharmacokinetics of nicorandil following oral administration have been described in healthy subjects.

## WHAT THIS STUDY ADDS

- This paper describes the differences in nicorandil pharmacokinetics between healthy subjects and acute heart failure patients.
- A population pharmacokinetic-pharmacodynamic model for nicorandil in acute heart failure patients is described using pulmonary artery wedge pressure as the biomarker.
- A rational guide for initial dosing of nicorandil to achieve a target effect on pulmonary artery wedge pressure was based on pharmacokinetic and pharmacodynamic principles.

## AIMS

The aims of the study were 1) to evaluate the pharmacokinetics of nicorandil in healthy subjects and acute heart failure (AHF) patients and 2) to evaluate the exposure-response relationship with pulmonary arterial wedge pressure (PAWP) in AHF patients and to predict an appropriate dosing regimen for nicorandil.

## METHODS

Based on the data from two healthy volunteer and three AHF patient studies, models were developed to characterize the pharmacokinetics and pharmacodynamics of nicorandil. PAWP was used as the pharmacodynamic variable. An asymptotic exponential disease progression model was used to account for time dependent changes in PAWP that were not explained by nicorandil exposure. The modelling was performed using NONMEM version V.

## RESULTS

The pharmacokinetics of nicorandil were characterized by a two-compartment model with linear elimination. CL, V<sub>1</sub> and V<sub>2</sub> in AHF patients were 1.96, 1.39 and 4.06 times greater than in healthy subjects. Predicted plasma concentrations were assumed to have an immediate concentration effect relationship on PAWP. An inhibitory E<sub>max</sub> model with E<sub>max</sub> of -11.7 mmHg and EC<sub>50</sub> of 423 µg l<sup>-1</sup> was considered the best relationship between nicorandil concentrations and PAWP. PAWP decreased independently of nicorandil exposure. This drug independent decline was described by an asymptotic decrease of 6.1 mmHg with a half-life of 5.3 h.

## CONCLUSIONS

AHF patients have higher clearance and initial distribution volume of nicorandil compared with healthy subjects. The median target nicorandil concentration to decrease PAWP by 30% is predicted to be 748 µg l<sup>-1</sup>, indicating that a loading dose of 200 µg kg<sup>-1</sup> and a maintenance dose of 400 µg kg<sup>-1</sup> h<sup>-1</sup> would be appropriate for the initial treatment of AHF.

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## Introduction

Acute heart failure (AHF) is associated with low cardiac output, tissue hypoperfusion, high pulmonary arterial wedge pressure (PAWP) and peripheral congestion. Vasodilators are used as first line therapy to improve the peripheral circulation and lower preload when hypoperfusion is associated with decreased blood pressure, signs of congestion and low diuresis [1].

The tablet formulation of nicorandil is widely used as an antianginal agent in European and Asian countries. In addition, nicorandil injection has been used for unstable angina in Japan and Korea. In a canine model, nicorandil has been shown to decrease left ventricular end diastolic pressure and increase cardiac output via both a nitrate like action (via an increase in cGMP) and the opening of ATP sensitive potassium channels [2]. In the treatment of patients with AHF, nicorandil reduces preload and afterload, and therefore the haemodynamic response. In comparison with nitrates, no tachyphylaxis has been reported with nicorandil [3, 4]. The pharmacokinetics after oral and IV administration are described elsewhere [5]. There are no known major active metabolites of nicorandil.

The immediate goal in AHF is to improve symptoms and stabilize the haemodynamic condition (e.g. by a decrease in PAWP and increase in cardiac output and/or stroke volume). While a change in cardiac output is dependent on the differential effects of vasodilators on arterial

and venous tone, PAWP is independently reduced by both mechanisms. Therefore, PAWP is an important endpoint for the evaluation of the therapeutic benefit of nicorandil.

The objectives of this pharmacokinetic-pharmacodynamic (PKPD) analysis were to determine the relationship between plasma nicorandil exposure and the PAWP response in AHF patients, and use the resulting model to propose an appropriate initial dosage regimen.

## Methods

The Institutional Research Review Committee approved all study protocols and informed consent was obtained from each patient prior to the trial. All studies were conducted according to the Declaration of Helsinki and Good Clinical Practice (GCP).

### Study designs

This present pharmacokinetic analysis was performed using five clinical studies, including two studies in healthy volunteers and three studies in AHF patients including acute exacerbation of chronic heart failure (Table 1).

*Bolus injection study for healthy volunteers* The primary objective of this study was to determine the safety, tolerability, and pharmacokinetic profile of nicorandil in healthy male subjects. Six healthy volunteers were enrolled into a

**Table 1**

Summary of patient characteristics at each study

Study	Bolus injection study Healthy volunteers	Bolus injection + infusion study Healthy volunteers	Bolus injection study Patients	Bolus injection + infusion study Patients	Long term infusion study Patients
<i>n</i>	5	6	28	46	20
Number of observation	105	175	159	79	100
Dose	6, 12, 18, 24 mg	Bolus: 12 mg Infusion: 6, 9, 12 mg h <sup>-1</sup> for 235 min	4, 8, 12, 18 mg	Bolus: 200 µg kg <sup>-1</sup> Infusion: 50–200 µg kg <sup>-1</sup> for 24 h	Bolus: 200 µg kg <sup>-1</sup> Infusion: 50–200 µg kg <sup>-1</sup> for 48 h
<b>Demographics</b>					
Age (years)	33.0 ± 7.7	41.2 ± 5.9	62.8 ± 12.8	65.1 ± 11.5	70.8 ± 8.4
Weight (kg)	62.6 ± 8.6	63.6 ± 6.4	58.6 ± 11.3	60.3 ± 10.7	61.8 ± 10.2
<b>Sex</b>					
Male	5	6	21	30	14
Female	0	0	7	16	6
<b>NYHA classification</b>					
II	–	–	3	10	4
III	–	–	10	12	6
IV	–	–	15	24	10
PAWP at predose (mmHg)	–	–	25.9 ± 6.4	26.9 ± 6.3	27.2 ± 7.4
CI at predose (l min <sup>-1</sup> m <sup>-2</sup> )	–	–	2.52 ± 0.70	2.47 ± 0.88	2.22 ± 0.43
<b>Cause</b>					
Ischaemic heart disease	–	–	11	16	6
Valvular heart disease	–	–	6	14	2
Hypertensive heart disease	–	–	4	7	2
Dilated cardiomyopathy	–	–	7	9	6

Data are shown as mean ± SD.

single bolus injection study, which was designed as a single-blind, ascending dose study. Nicorandil was administered intravenously at a dose of 6, 12, 18 or 24 mg over 5 min. Every subject was administered four doses of nicorandil. One subject dropped out after the first dosing because of SA node block, which was judged not to be related to nicorandil.

*Bolus injection and infusion study for healthy volunteers* The primary objective of this study was to determine the safety, tolerability, and pharmacokinetic profile of nicorandil in healthy male subjects during and after infusion. Nine healthy volunteers were enrolled in a single-blind, ascending dose combination study of a rapid 'bolus' injection followed by a constant rate infusion. Nicorandil (12 mg) was injected over 5 min followed by an infusion rate of 6, 9 or 12 mg h<sup>-1</sup> of nicorandil for 235 min. Two subjects dropped out one because of an increase in erythrocyte sedimentation rate and fever as adverse events and the other withdrew voluntarily.

*Bolus injection study for AHF patients* This was an open-label non-randomized study designed to assess the safety, tolerability, and pharmacokinetics of intravenously administered nicorandil following bolus injection doses in AHF patients. Patients with AHF were enrolled if they satisfied the following inclusion criteria: (i) PAWP or diastolic pulmonary arterial pressure, if PAWP was impossible to measure, was higher than 18 mmHg and was stable for at least 15 min, (ii) age between 20 and 79 years old. Twenty-eight patients were separated into four cohorts (4, 8, 12 and 18 mg) and administered nicorandil. The bolus injection was administered over 1 to 5 min.

*Bolus injection and infusion study for AHF patients* This was an open-label non-randomized study designed to assess the safety, tolerability, and pharmacokinetics of nicorandil administered by infusion following bolus injection in AHF patients. Patients with AHF were enrolled if they satisfied the following inclusion criteria: (i) PAWP or diastolic pulmonary arterial pressure, if PAWP was impossible to measure, higher than 18 mmHg, (ii) age between 20 and 79 years old. A total of 46 patients were divided into five groups: a bolus injection of 200 µg kg<sup>-1</sup> nicorandil was injected followed by infusion at a rate of 50, 100, 150, 200 or 250 µg kg<sup>-1</sup> h<sup>-1</sup>. The bolus injection was administered over 5 min, and infusion was performed for 6 or 24 h, if possible.

Treatment with digitalis glycosides and fluid transfusion continued without changing the dosage during the study. Vasodilators, diuretics, inotropic agents, sulfonamide, hypoglycaemic agents and all other concomitant medications were withheld during both studies.

*Long-term infusion study* This was an open-label non-randomized study designed to assess the safety, tolerability, and pharmacokinetics during long-term infusion of

nicorandil following bolus doses in AHF patients. Patients with AHF were enrolled if they satisfied the following inclusion criteria: (i) PAWP or diastolic pulmonary arterial pressure, if PAWP was impossible to measure, higher than 15 mmHg, (ii) age over 20 years old. Twenty-three patients with AHF were administered nicorandil intravenously at a dose of 200 µg kg<sup>-1</sup> over 5 min followed by a continuous infusion at a rate of 200 µg kg<sup>-1</sup> h<sup>-1</sup> for 48 h. Concomitant medications were allowed to be used during the study except for oral doses of nicorandil and sildenafil citrate.

### Collection of blood samples

*Bolus injection study for healthy volunteers* Blood samples were collected at predose and at 5, 15, 30 min, 1, 2, 4, 5, 8, 12, 24 h after the dose in single bolus injection dose study.

*Bolus injection and continuous infusion study for healthy volunteers* Blood samples were collected at predose and at 5, 15, 30 min, 1, 2, 4, 4.5, 8, 12, 24 h after the dose in the bolus injection plus infusion dose study.

*Bolus injection study for AHF patients* Blood samples were collected at predose and 0.25, 0.5, 1, 1.5, 2 and 3 h after the dose in the single bolus injection dose study except for the dose of 18 mg when samples collected at predose and at 0.25, 0.5 and 1 h after the dose. PAWP was measured at the same time as blood sampling in the bolus injection dose study.

*Bolus injection and continuous infusion study for AHF patients* In the combined bolus injection plus infusion study, blood samples were collected at predose and 1 and 6 h. PAWP was measured predose and at 0.25, 0.5, 1, 2, 4 and 6 h.

*Long-term infusion study* Blood samples were collected at predose and 2, 6, 12, 24, 48 h after start of dose. PAWP was measured at 2, 24 and 48 h.

### Assay of nicorandil in plasma

Nicorandil in plasma was quantified by HPLC [6]. For all studies except for the long-term infusion study, the lower limit of quantification (LLOQ) was 3 ng ml<sup>-1</sup> (defined by the coefficient of variation of replicate samples less than 20%). The within day coefficient of variation of the assay ranged from 10.12% (3 ng ml<sup>-1</sup>) to 2.55% (100 ng ml<sup>-1</sup>). Nicorandil in plasma was measured at Mitsubishi Kagaku Bio-Clinical Laboratories, Inc (Tokyo, Japan) and Chugai Pharmaceutical Co., Ltd. (Tokyo, Japan).

For the long-term infusion study, a slightly modified assay method for determination of nicorandil concentrations in plasma was applied because the solid phase extraction column was no longer obtainable. This method was developed by Japan Clinical Laboratories, Inc. (Osaka, Japan). By this method, the LLOQ was 5 ng ml<sup>-1</sup> and the

coefficient of variable (CV) value at the LLOQ was less than 15%. The within day CV of the assay ranged from 4.6% (5 ng ml<sup>-1</sup>) to 2.4% (1000 ng ml<sup>-1</sup>).

Both of those HPLC methods have almost the same recovery ratio. These are 76.6–89.8% in the concentration range of 3 ng ml<sup>-1</sup> to 200 ng ml<sup>-1</sup> for the first method and 78.8–80.0% in the range of 5 ng ml<sup>-1</sup> to 1000 ng ml<sup>-1</sup> for the modified method applied to the latest study, respectively.

Data below the LLOQ of plasma concentration were excluded from the population pharmacokinetic analysis.

### Measurement of PAWP

PAWP was measured using a Swan-Ganz catheter. If for technical reasons it was not possible to measure PAWP then pulmonary arterial diastolic pressure was recorded instead.

### Models

**Model estimation** Nonlinear mixed effect models using NONMEM (Version V; GloboMax LLC, MD, USA) were developed to characterize the pharmacokinetics and pharmacodynamics of nicorandil in the healthy volunteer and patient population. All models were fitted using the first-order conditional estimation (FOCE) method with interaction. NONMEM was compiled by Intel Visual Fortran (Version 9; Intel Corporation, CA, USA) on a Windows XP operating system (Microsoft Corporation, WA, USA).

Fixed and random effect model building was performed based on the change in objective function and examination of the model predictions. The covariance between random effects was investigated.

A visual predictive check was performed by simulating 1000 virtual observations at each time point using the final model and its parameter estimates. Parameter uncertainty was evaluated by a non-parametric bootstrap procedure.

The pharmacokinetic model was developed separately and then used with fixed parameter values to explore the disease progression and pharmacodynamic models. The concentration observations were included in the data set even though the PK parameters were fixed (PPPD method [7]). The final models were tested with simultaneous estimation of all parameters. The simultaneous method was used for the bootstrap runs.

### Pharmacokinetics of nicorandil

The duration of bolus injections and constant rate infusions of nicorandil were recorded on the case report form. It was assumed that the dose was infused at a constant rate over the recorded duration. Input was assumed to be zero-order with rate  $k_0$  calculated using the administered dose and infusion duration. A one compartment model with clearance (CL) and distribution volume (V1) and a two compartment model with clearance (CL), intercompartmental clearance (Q), central compartment volume (V1)

and peripheral compartment volume (V2) were evaluated to describe nicorandil disposition.

### Pharmacodynamics of the effect of nicorandil on PAWP

There was no clear evidence of a delay between PAWP changes and changes in plasma concentration (see Figure 6). Any delay was expected to be short because nicorandil acts on blood vessels so that the distributional delay from plasma to the extracellular fluid at the blood vessel calcium channel was expected to be at most a matter of minutes. The vasorelaxation effect of nicorandil occurs rapidly *in vitro* [8] so we did not expect this to introduce detectable delays in the observed response. Finally, intracellular responses e.g. cyclic GMP are typically occurring in seconds. Because all of these processes reach a new steady state quickly it may be difficult to detect a delay due to these mechanisms. An empirical effect compartment model was tested to estimate the magnitude of delay and see if it improved the ability to predict PAWP time course.

The interaction between nicorandil concentration,  $C_e(t)$ , and change in PAWP was assumed to be determined immediately by plasma concentration or the predicted effect compartment concentration. Linear (Equation 1) and  $E_{max}$  models (Equation 2) were tested to see which gave the better fit.

$$PD_{lin}(t) = Slope \cdot C_e(t) \quad (1)$$

$$PDE_{max}(t) = \frac{E_{max} \cdot C_e(t)}{EC_{50} + C_e(t)} \quad (2)$$

### Disease progression

Two models were evaluated to describe changes in PAWP unrelated to nicorandil concentration. These models provided an empirical description of the time course of PAWP. Because PAWP is a biomarker for heart failure disease status we considered them disease progress models. The first model assumed that PAWP decreases linearly (linear model) over the duration of observation from a baseline value ( $S_0$ ) with slope  $\alpha$  (Equation 3) [9].

The second model assumed an asymptotic exponential change (exponential model) in PAWP from a baseline to a new steady state value ( $S_{SS}$ ) with a time course described by a half-life of progression ( $T_{prog}$ ). In both cases the effect of nicorandil was assumed to produce a time varying offset,  $PD(t)$ , to the disease progression curve [9].

$$PAWP(t) = S_0 + \alpha \cdot t + PD(t) \quad (3)$$

$$PAWP(t) = S_0 + (S_{SS} - S_0) \times (1 - \exp(-\ln(2)/T_{prog} \times t)) + PD(t) \quad (4)$$

### Covariate effects

Fixed effect models for between subject variability in parameters were used to predict group specific param-

eters from the population standard estimate [10]. Size differences were based on a standard weight of 70 kg. Differences in CL, Q, V1 and V2 were assumed to be explained in part by an allometric function of weight [11] e.g. Equation 5.

$$CL_{GRP} = CL_{POPSTD} \cdot \left( \frac{Wt}{Wt_{STD}} \right)^{3/4} \quad (5)$$

Differences in CL, Q, V1 and V2 between patients and healthy subjects were investigated using models such as equation 6. FCL is the fractional difference in clearance between patients with AHF and healthy subjects.

$$CL_{POP\_patients} = CL_{POP\_HV} \cdot FCL \quad (6)$$

No other covariates were evaluated to describe differences between the subjects in these studies.

### Random effects

*Between subject and within subject variability in parameters* Population parameter variability (PPV) in pharmacokinetics and pharmacodynamics was described by assuming a log-normal distribution for random differences in parameters. PPV was partitioned between (BSV) and within (WSV) subject variability by estimating parameters within different occasions (see [12, 13] for details). An occasion was defined as each time a dose was given and followed by observations. The individual and occasion specific parameter for subject *i* on the *k*th occasion was obtained from the group parameter estimate. This is illustrated for CL in equation 7.

$$CL_{i,k} = CL_{GRP} \cdot \exp(\eta_{BSV,i} + \eta_{WSV,i,k}) \quad (7)$$

The  $\eta$  random effects were assumed to arise from a normal distribution with mean 0 and standard deviation BSV for between subject variability and WSV for within subject variability. The variance of BSV and WSV was estimated. The covariance of BSV was estimated in order to describe the within individual correlation of random effects.

*Residual unidentified variability in observations* Residual unidentified variability (RUV) for pharmacokinetic data was described by proportional (RUV\_CV) and additive (RUV\_SD) random differences of the observations from the predictions. RUV for pharmacodynamic data was described by additive random differences of the observations from predictions. The proportional component was predicted from the prediction for the *j*th observation in the *i*th individual (PRED<sub>*i,j*</sub>) (Equation 8). Both RUV\_CV and RUV\_SD were estimated from observations of nicorandil. Only RUV\_SD was estimated from PAWP observations.

Between subject parameter variability in RUV was described by a random effect ( $\eta$ ) which was assumed to arise from a normal distribution with mean 0 and standard deviation PPV\_RUV [14]. A random effect ( $\epsilon$ ) for each obser-

vation was assumed to arise from a normal distribution with mean 0 and unit standard deviation.

$$SD = \text{SQRT}((\text{PRED}_{i,j} \cdot \text{RUV\_CV})^2 + (\text{RUV\_SD})^2) \cdot \text{EXP}(\eta_{PPV\_RUV,i}) \quad (8)$$

$$Y_{i,j} = \text{PRED}_{i,j} + SD \cdot \epsilon$$

## Results

### Demographics

Table 1 presents a summary of demographics in healthy volunteers and patients. Data were available from 105 subjects. Eleven healthy volunteers contributed nicorandil concentrations only. The data from healthy volunteers was used to establish the PK model of nicorandil. Ninety-four subjects contributed observations of nicorandil concentrations and PAWP. There were 618 nicorandil concentration observations and 559 PAWP observations.

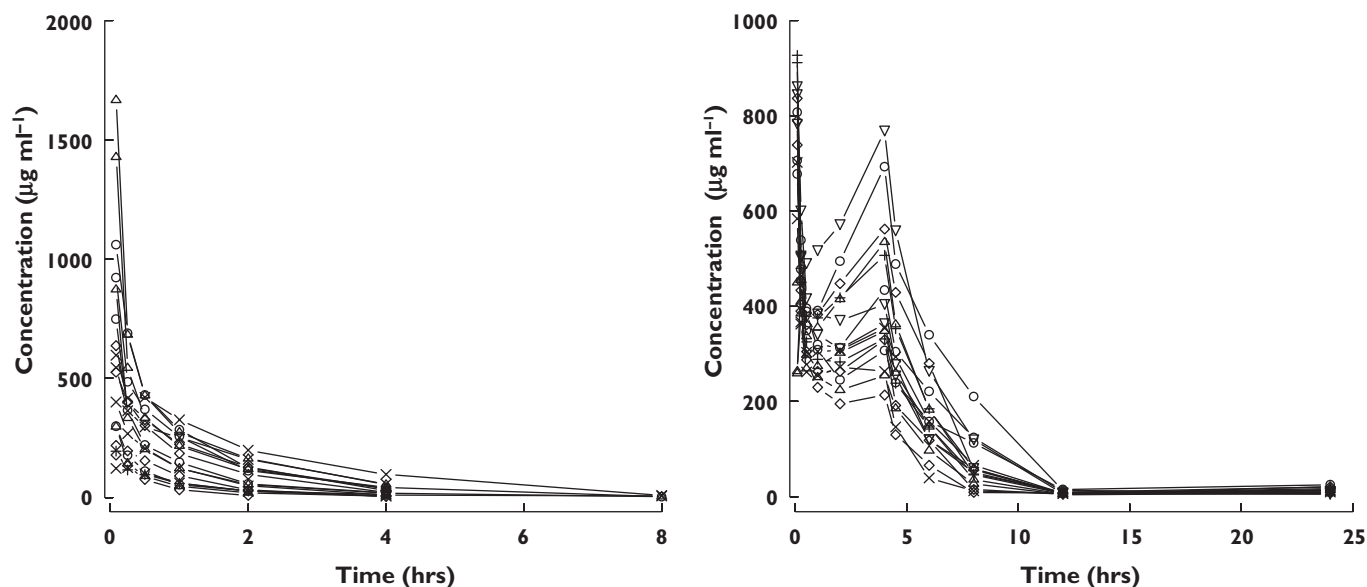
### Pharmacokinetics of nicorandil

Individual pharmacokinetic profiles of nicorandil after intravenous injection to healthy volunteers are shown in Figure 1 and those in AHF patients in Figure 2. The best final pharmacokinetic model was a two compartment model. Goodness of fit plots using the two compartment model and data from healthy subjects and AHF patients are shown in Figure 3. The results of the visual predictive check in AHF patients are shown in Figures 4 and 5. The visual predictive check simulations are based on all the infusion rates and durations in the observed patients. Because of the variety of doses and rates, the profile shown in the figures should only be used to compare with the observed concentrations. It does not reflect any specific dosing regimen.

The clearance of nicorandil was nearly doubled in patients with AHF compared with healthy subjects (Table 2). The distribution volume of nicorandil in the central compartment was increased by 40% in AHF patients. Intercompartmental clearance of nicorandil was halved in AHF patients. The distribution volume of nicorandil in the peripheral compartment was four times greater in patients with AHF than in healthy subjects.

### Pharmacodynamic analysis of nicorandil

The relationship between PAWP and plasma concentration of nicorandil is shown in Figure 6. The effect compartment half-life and its variability were estimated to be 2.2 min with very small between patient variability. The NONMEM run finished with rounding errors and less than three significant digits and an objective function fall of 8.9. It was decided that there was little evidence to support the additional complexity of a model for delay in onset of effect. We concluded that PAWP decreased rapidly after the administration of 12 or 18 mg kg<sup>-1</sup> of nicorandil, with a negligible



**Figure 1**  
Individual plasma concentrations of nicorandil in healthy volunteers

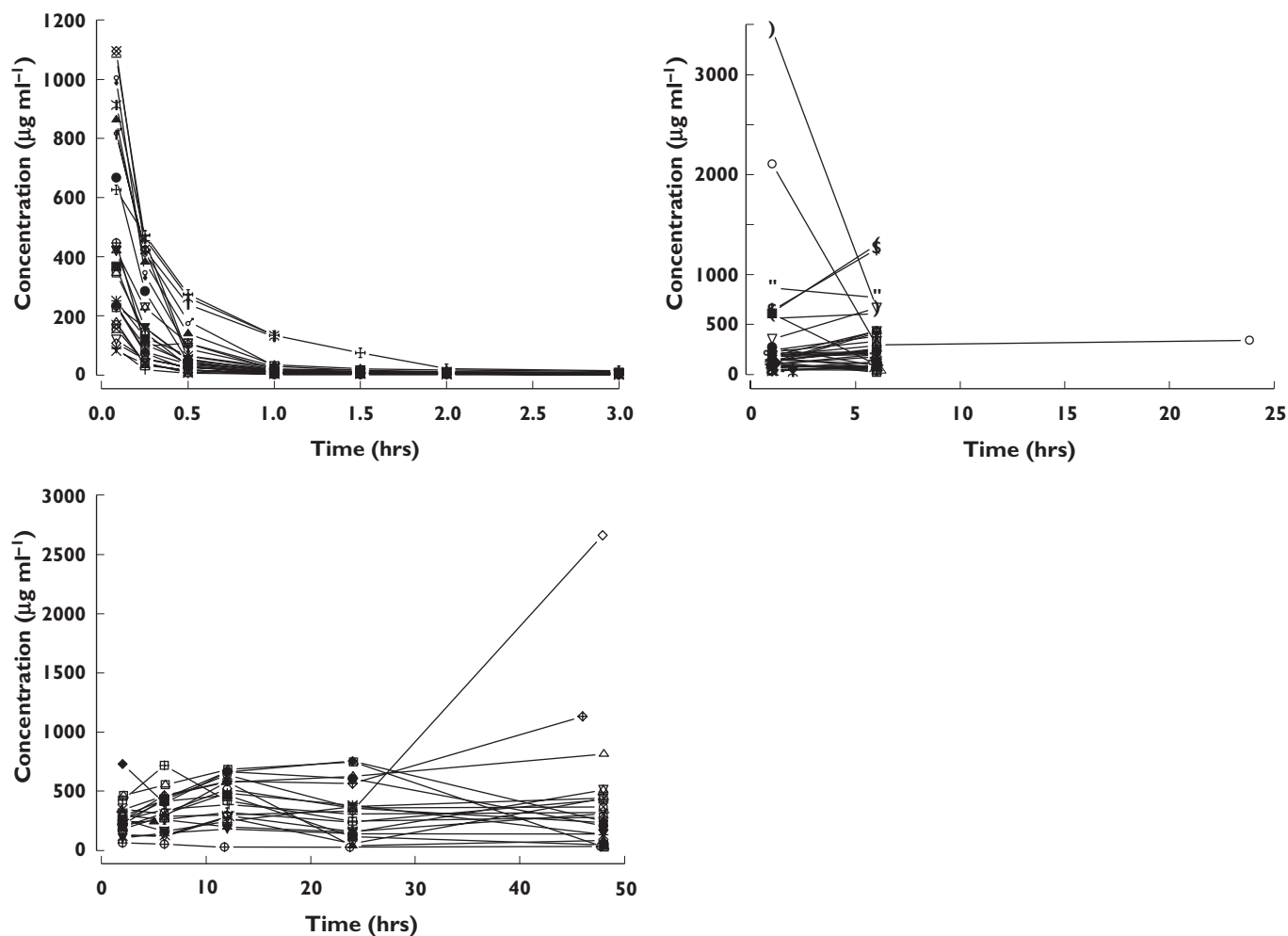
**Table 2**  
Pharmacokinetic and pharmacodynamic structural model parameter estimates for the effect of nicorandil on PAWP using model 10. Bootstrap coefficient of variation (standard deviation/median) and empirical 90% confidence interval

Statistic	Description	Median	Units	CV %	Confidence interval	
					5%	95%
POP_S0	Baseline PAWP	25.6	mmHg	2.7	24.6	26.8
POP_S <sub>ss</sub>	Steady state PAWP	19.5	mmHg	10.0	16.5	22.7
POP_TPROG	Progress half-life	5.83	h	69.4	0.920	11.9
POP_E <sub>max</sub>	Maximum effect of nicorandil on PAWP	-11.7	mmHg	58.7	-30.0	-7.48
POP_EC <sub>50</sub>	Nicorandil concentration at 50% of E <sub>max</sub>	423	µg l <sup>-1</sup>	107.1	165	1552
POP_CL	Nicorandil clearance	26.3	l h <sup>-1</sup> 70 kg <sup>-1</sup>	13.5	21.9	31.5
POP_V1	Central volume of distribution	18.1	l 70 kg <sup>-1</sup>	14.8	14.9	23.3
POP_Q	Intercompartmental clearance	71.6	l h <sup>-1</sup> 70 kg <sup>-1</sup>	76.9	54.5	203
POP_V2	Peripheral volume of distribution	24.1	l 70 kg <sup>-1</sup>	6.6	21.1	25.4
FCL	Fractional CL change in heart failure	1.94		25.0	1.03	2.63
FV1	Fractional V1 change in heart failure	1.39		17.0	1.05	1.81
FQ	Fractional Q change in heart failure	0.519		42.8	0.192	0.891
FV2	Fractional V2 change in heart failure	4.06		219.1	1.83	25.3

delay in PAWP response. The PAWP changes in individual subjects are shown in Figure 7. There was evidence that the achieved concentrations were approaching those required for maximum effect because the E<sub>max</sub> model was preferred over the linear model based on improvement in the objective function (compare model 12 with model 11 in Table 3).

The between subject random effects were correlated. Inclusion of the covariance between S<sub>0</sub>, S<sub>ss</sub>, and EC<sub>50</sub> improved the objective function (compare model 13 with model 11 in Table 3).

Allowing PAWP to vary with time, independently of nicorandil exposure, further improved the objective function (compare model 17 with model 16 in Table 3). An asymptotic disease progress model described the changes in PAWP better than a linear model (compare model 16 with model 13 in Table 3). The disease progression model predicted that PAWP changes slowly over the study observation period independently of nicorandil exposure. A change of 6.1 mmHg (S<sub>0</sub>-S<sub>ss</sub>) is the asymptotic prediction of the decrease in PAWP from baseline independent of nicorandil exposure.



**Figure 2**

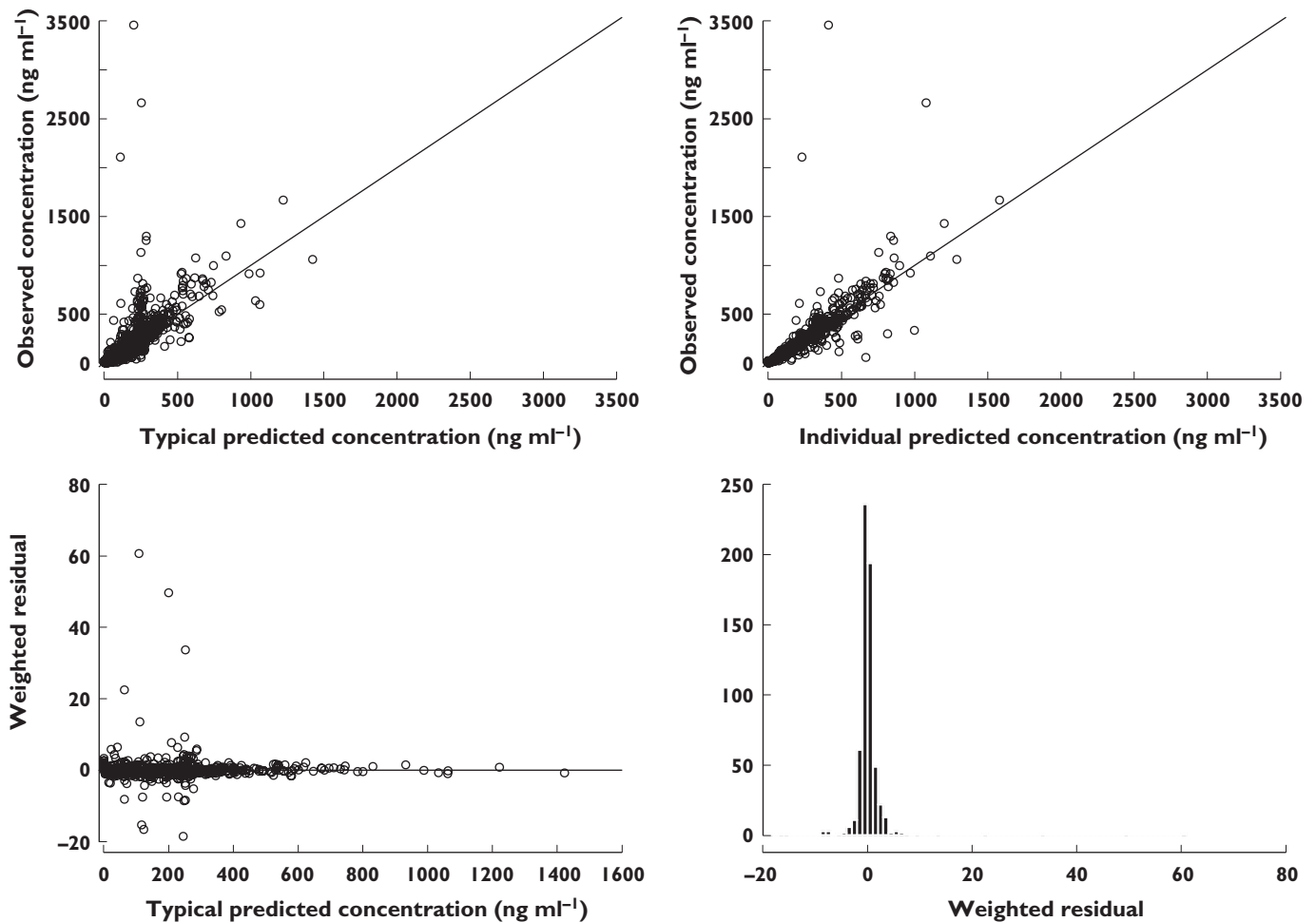
Individual plasma concentration profiles of nicorandil following administration to acute heart failure patients. Left upper panel: bolus injection of nicorandil at a dose of 4, 8, 12 and 18 mg kg<sup>-1</sup>. Right upper panel: 6 h or 24 h infusion of nicorandil at a dose of 50, 100, 150, 200 and 250 µg kg<sup>-1</sup> h<sup>-1</sup> following a bolus injection of nicorandil at a dose of 200 µg kg<sup>-1</sup>. Left lower panel: 48 h infusion of nicorandil at a dose of 200 µg kg<sup>-1</sup> h<sup>-1</sup> following a bolus injection of nicorandil at a dose of 200 µg kg<sup>-1</sup>

**Table 3**

Model building table for nicorandil pharmacodynamics and disease progress

Model	Disease progress	Drug effect	Random effects	Estimation	Obj	Sig
10	Exponential	E <sub>max</sub>	Covariance of S <sub>0</sub> , SS, EC <sub>50</sub>	Simultaneous	7600.48	5.9
11	Exponential	E <sub>max</sub>	Covariance of S <sub>0</sub> , SS, EC <sub>50</sub>	Sequential	7601.34	6.5
12	Exponential	Linear	Covariance of S <sub>0</sub> , SS, EC <sub>50</sub>	Sequential	7624.16	5.4
13	Exponential	E <sub>max</sub>	No covariance	Sequential	7624.92	5.9
14	Linear	Sigmoid E <sub>max</sub>	Covariance of S <sub>0</sub> , alpha, E <sub>max</sub> , EC <sub>50</sub>	Sequential	7634.66	6.6
15	Linear	E <sub>max</sub>	Covariance of S <sub>0</sub> , alpha, E <sub>max</sub> , EC <sub>50</sub>	Sequential	7634.80	6.3
16	Linear	E <sub>max</sub>	No covariance	Sequential	7639.33	5.9
17	None	E <sub>max</sub>	Covariance of S <sub>0</sub> , E <sub>max</sub> , EC <sub>50</sub>	Sequential	7664.96	.

Obj, NONMEM objective function value; Sig, NONMEM estimate of minimum number of significant digits in the parameter estimates.



**Figure 3**

Goodness of fit plots under the final pharmacokinetic model for nicorandil. Lines in upper right and left panel show unity

The objective function did not change appreciably when both the PK and PD components were fitted simultaneously. Model 10 was considered the best PKPD model describing the nicorandil concentrations and response of PAWP.

For the final PKPD model the goodness of fit plots are shown in Figure 8 and the visual predictive check in Figures 9 and 10. Final parameter estimates calculated by a non-parametric boot strap method are shown in Table 2 and random effect parameters are shown in Table 4. The maximum predicted effect of nicorandil ( $E_{\max}$ ) was  $-11.7$  mmHg and the nicorandil concentration at 50% of  $E_{\max}$  was  $423 \mu\text{g ml}^{-1}$ .

### The target effect and target concentration of nicorandil

The observed baseline PAWP values in the bolus, bolus and infusion, and long-term studies were 25.9, 26.9 and 27.2 mmHg, respectively (Table 1). A decrease of 30% in PAWP from baseline due to nicorandil was proposed as the target effect. A target decrease of 30% in PAWP would

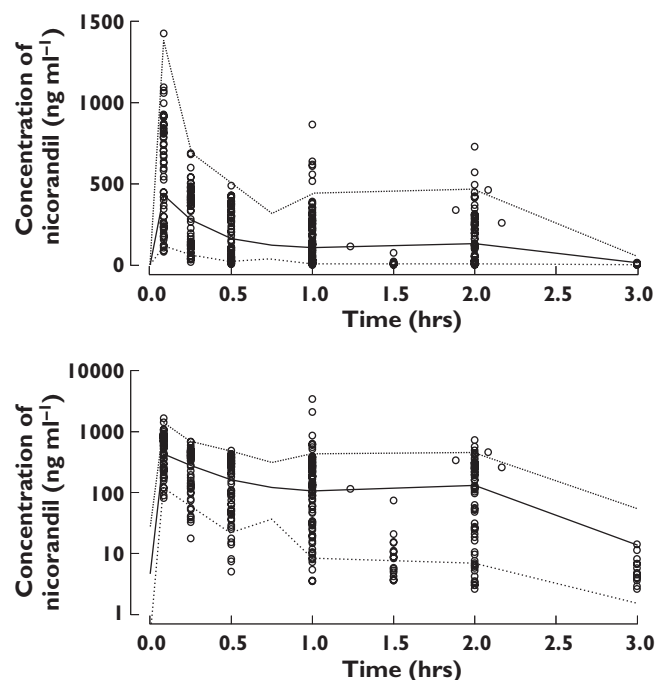
reduce PAWP to close to 18 mmHg (i.e. 18.1, 18.8 and 19.0 mmHg, respectively). This is consistent with current treatment guidelines [1]. Further decreases in PAWP due to factors unrelated to nicorandil would produce further lowering over the following 24 h. The target concentration of nicorandil to achieve this target initial PAWP, was predicted for each patient using maximum *a posteriori* Bayesian estimates from the final PKPD model. The target concentration was obtained using the  $E_{\max}$  model and solving for the concentration needed to produce a 30% fall in PAWP. The loading dose was predicted by multiplying the target concentration by the central compartment volume and the maintenance dose rate was predicted by multiplying the target concentration by the elimination clearance. This is a simplification of the two compartment model and ignores the early drop and subsequent rise in concentrations reflecting equilibration of the central and peripheral compartments. The median and 90% intervals of the individual patient predicted doses are shown in Table 5. The median target concentration of nicorandil to decrease PAWP by 30% was estimated to be  $748 \mu\text{g/l}$  and the median loading



**Table 4**

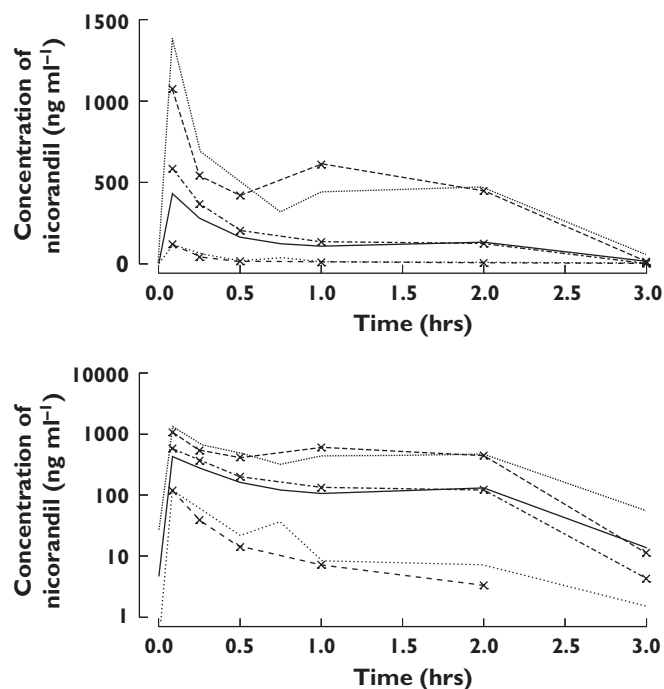
Pharmacodynamic random effects model parameter estimates for the effect of nicorandil on PAWP using model 10. Bootstrap coefficient of variation (standard deviation/median) and empirical 90% confidence interval

Statistic	Description	Median	CV %	Confidence interval	
				5%	95%
PPV_S0	Population parameter variability in S0	0.210	8.5	0.180	0.238
PPV_S <sub>ss</sub>	Population parameter variability in S <sub>ss</sub>	0.320	23.9	0.233	0.431
PPV_EC <sub>50</sub>	Population parameter variability in EC <sub>50</sub>	0.879	58.4	0.075	1.76
BSV_CL	Between subject variability in CL	0.686	19.0	0.523	0.941
BSV_V1	Between subject variability in V1	0.301	26.2	0.214	0.453
BSV_Q	Between subject variability in Q	0.414	82.1	0.067	1.167
BOV_CL1	Between occasion variability in CL	0.199	24.7	0.116	0.279
R12	Correlation of S0 and S <sub>ss</sub>	0.864	16.1	0.621	1.00
R23	Correlation of S <sub>ss</sub> and EC <sub>50</sub>	0.054	692.5	-10.57	0.651
R78	Correlation of CL and V1	0.257	104.0	-0.1673	0.709
R89	Correlation of V1 and Q	0.957	37.0	0.3044	1.00
PPV_RUVFX	Population parameter variability in PAWP residual error	0.308	42.3	0.010	0.487
RUV_SDFX	Standard deviation of PAWP residual error	2.5	6.9	2.22	2.79
PPV_RUVCP	Population parameter variability in nicorandil residual error	0.716	27.3	0.419	1.05
RUV_CVCP	Coefficient of variation of nicorandil residual error	0.212	12.9	0.172	0.260
RUV_SDCP	Standard deviation of nicorandil residual error	6.82	38.0	3.73	12.0



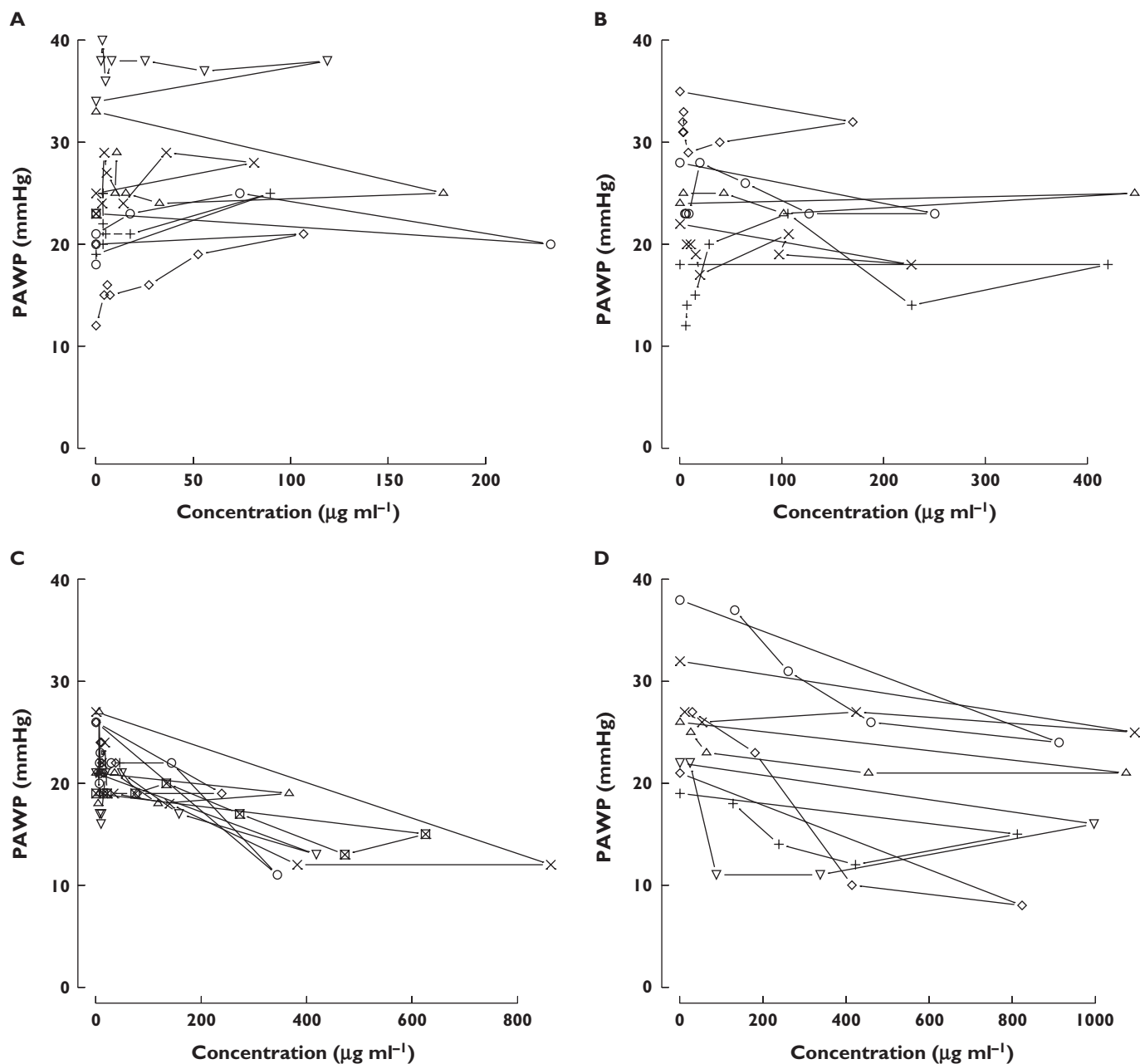
**Figure 4**

Visual predictive check of PKPD model 10 for nicorandil concentration in acute heart failure patients (symbols are observation, median is thick line, 90% prediction intervals are thin lines). Low (-----), median (—), high (.....), observed (O)



**Figure 5**

Visual predictive check of PKPD model 10 for nicorandil concentration in acute heart failure patients (lines with symbols are observations and without symbols are predictions; median is thick line, 90% prediction intervals are thin lines). Low (-----), median (—), high (.....), OBS low (----), OBS median (-----), OBS high (---)



**Figure 6**

Concentration–effect (PAWP) plots of nicorandil. These data were obtained from a bolus injection study of patients with AHF. PAWP was measured using a Swan-Ganz catheter. Concentrations of nicorandil were measured by HPLC. Each plot shows individual data. Panels A, B, C, and D show a 4, 8, 12 and 18 mg kg<sup>-1</sup> bolus dose of nicorandil

dose and maintenance infusion rate required to achieve the target concentration were estimated to be 230 µg kg<sup>-1</sup> and 412 µg kg<sup>-1</sup> h<sup>-1</sup>.

## Discussion

We performed a PKPD analysis to determine the relationship between plasma nicorandil concentration and haemodynamic changes in acute heart failure patients in order to predict an appropriate loading and maintenance dose of nicorandil. Data from five studies, which included 11 healthy subjects and 94 patients with AHF, were analyzed using a nonlinear mixed effects modelling approach.

The results of this present analysis are consistent with previous reports, that nicorandil is eliminated rapidly from plasma in human studies [15]. A surprising finding was the increase in the plasma clearance of nicorandil in patients

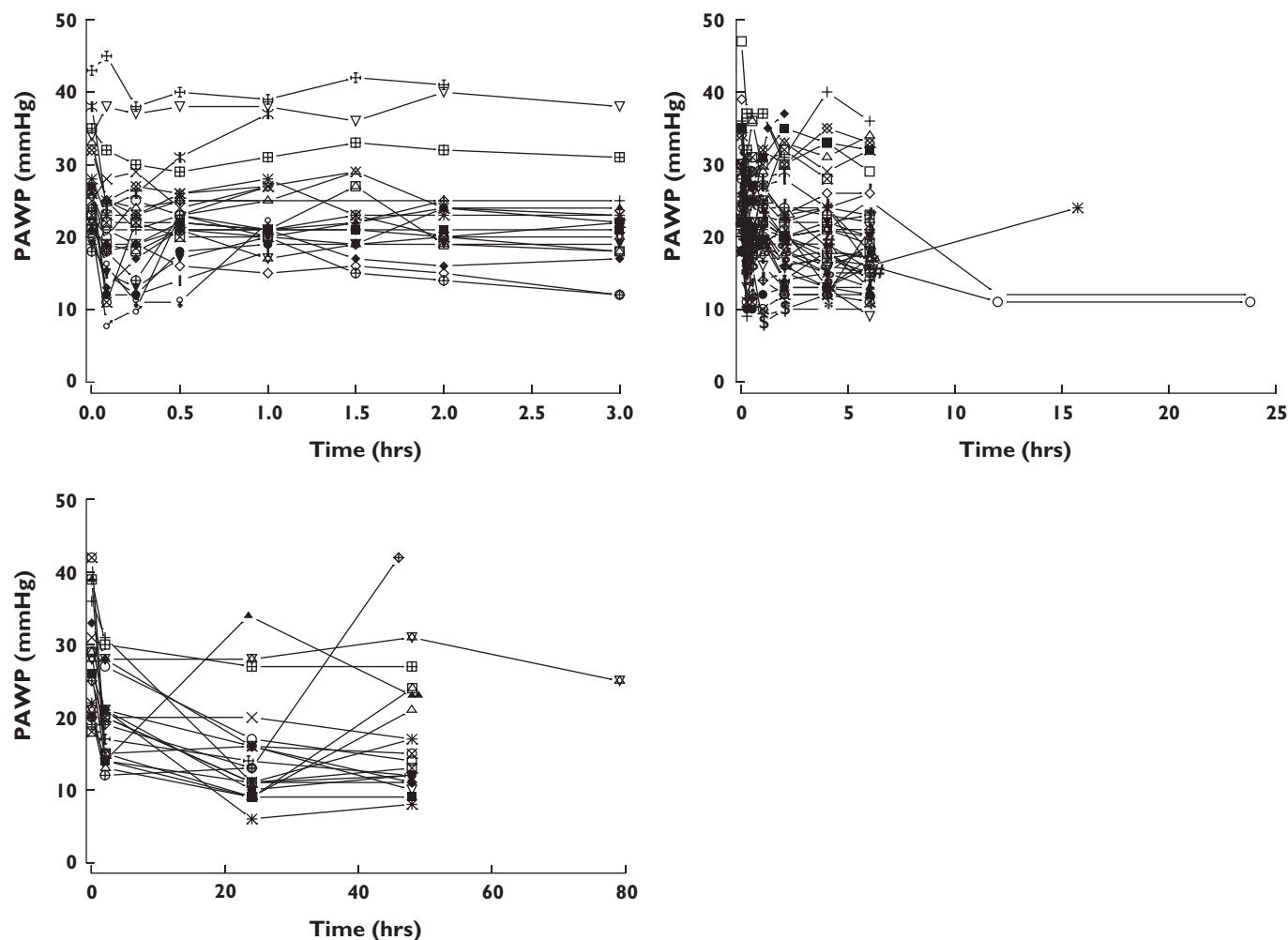
modulatory changes in acute heart failure patients in order to predict an appropriate loading and maintenance dose of nicorandil. Data from five studies, which included 11 healthy subjects and 94 patients with AHF, were analyzed using a nonlinear mixed effects modelling approach.

**Table 5**

Post hoc target effect and dose statistics (94 subjects of whom 84 were predicted to be able to reach the target PAWP)

Statistic	Target PAWP (mmHg)	Target concentration ( $\mu\text{g l}^{-1}$ )	Loading dose ( $\mu\text{g kg}^{-1}$ )	Maintenance rate ( $\mu\text{g kg}^{-1} \text{h}^{-1}$ )
Median	-7.5	747.8	230.4	412.5
Lower 5% CI	-10.9	147.0	33.3	78.8
Upper 95% CI	-5.8	3778.6	1229.5	3543.5

CI, Confidence interval.



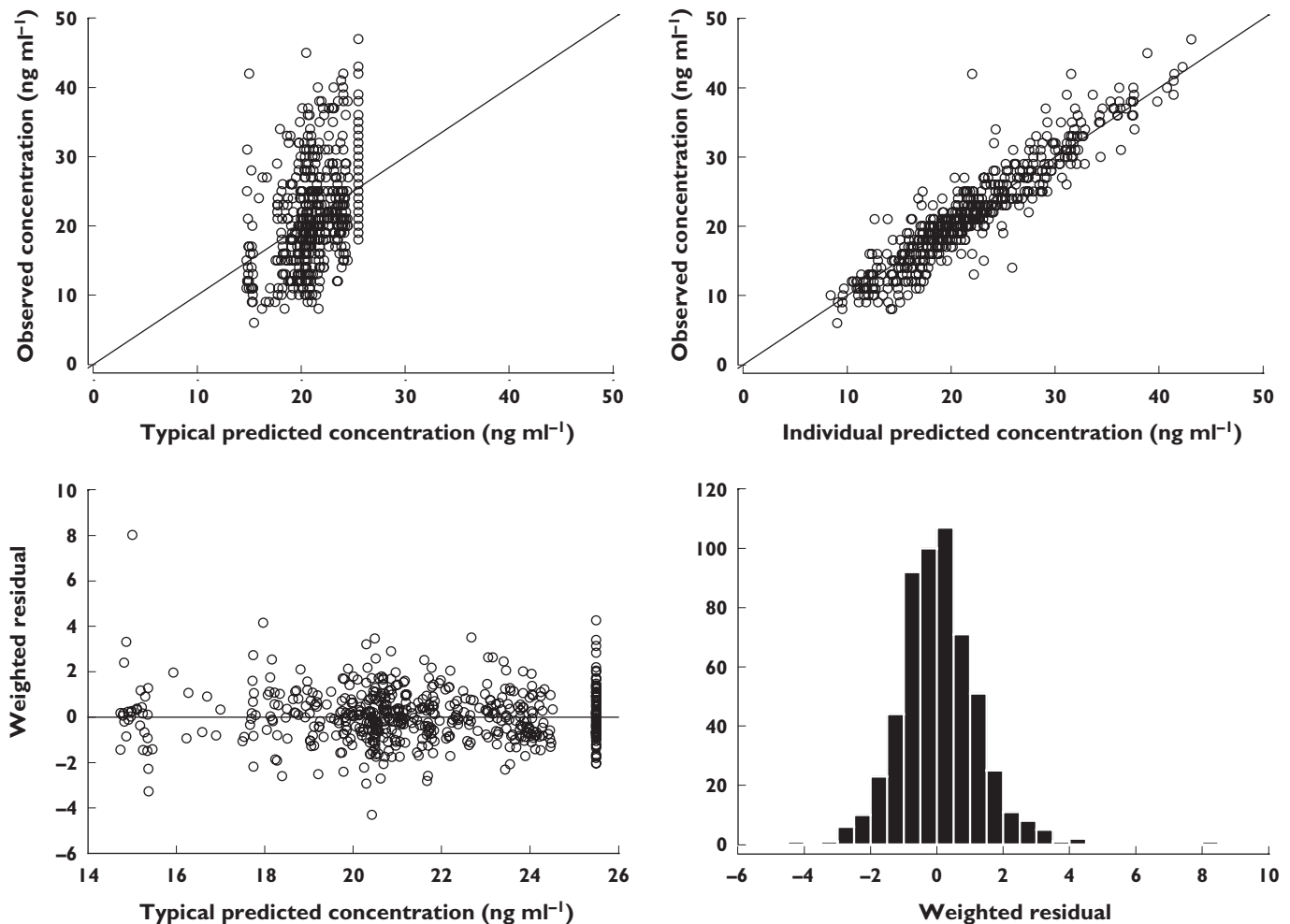
**Figure 7**

Individual PAWP profiles of nicorandil following administration to acute heart failure patients. Left upper panel: bolus injection of nicorandil at a dose of 4, 8, 12 and 18  $\text{mg kg}^{-1}$ . Right upper panel: 6 h or 24 h infusion of nicorandil at a dose of 50, 100, 150, 200 and 250  $\mu\text{g kg}^{-1} \text{h}^{-1}$  following a bolus injection of nicorandil at a dose of 200  $\mu\text{g kg}^{-1} \text{h}^{-1}$ . Left lower panel: 48 h infusion of nicorandil at a dose of 200  $\mu\text{g kg}^{-1} \text{h}^{-1}$  following a bolus injection of nicorandil at a dose of 200  $\mu\text{g kg}^{-1}$

with AHF compared with healthy subjects (Table 2). A decrease in clearance due to lower hepatic blood flow and impaired hepatic function would have been expected, and we cannot offer a plausible mechanistic explanation for an increase in clearance in AHF. There did seem to be an increase in central volume and a decrease in intercompartmental

clearance in AHF which could be explained by venous distension and reduced tissue perfusion rate in AHF patients.

The lack of detectable delay in onset of effect suggests nicorandil reaches these sites rapidly and quickly changes vascular resistance. Other vasodilator drug



**Figure 8**

Goodness of fit plots for the final pharmacokinetic-pharmacodynamic model (model 10)

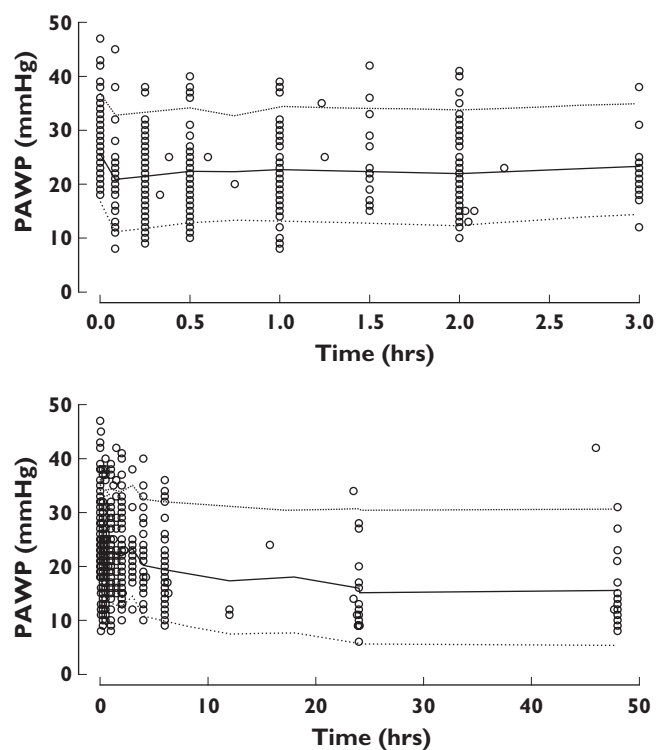
effects have been described using similar models. The pharmacokinetic-pharmacodynamic relationship characterizing the haemodynamic effects of a calcium antagonist has been described by an immediate effect with an  $E_{\max}$  model [16, 17]. Similarly, the effect of 1,3-glycerol nitrate on blood pressure was analyzed assuming an immediate effect with an inhibitory  $E_{\max}$  model [18].

We have demonstrated that there is a component of the time course of PAWP in AHF which is unrelated to exposure. It seems plausible that such an effect would occur in unstable patients admitted to hospital with heart failure. However, the reasons for the slow change in PAWP are only speculative and we see no rational basis for believing that other models such as a turnover model would be superior to an empirical description of this phenomenon.

The disease progress model we used is based on a description of changes in PAWP that appear to be independent of nicorandil exposure. In the absence of a placebo it is impossible to distinguish true progression from effects due to the drug without some assumptions based on prior

information. We expect nicorandil effects to be rapid (see above). The slow (half-life 5.8 h) change in PAWP predicted from the model appears to be independent of exposure to nicorandil. The disease progress phenomenon which reaches a steady state after 24 h (four half-lives) seems a plausible description for PAWP changes expected in patients with unstable AHF related to other factors associated with hospitalization and treatments other than nicorandil e.g. diuretics.

We used the pharmacodynamic analysis to predict an appropriate loading and maintenance dose of nicorandil. The major adverse events related to nicorandil in these studies were headache and hypotension. There was no obvious relationship between plasma concentration of nicorandil and the incidence of hypotension. The estimated plasma concentration of nicorandil to achieve a 30% decrease in PAWP was  $748 \text{ ng ml}^{-1}$ . This is similar to the concentration of nicorandil ( $850.6 \text{ ng ml}^{-1}$ ) required to decrease the left ventricular end-diastolic pressure by ~30% in dogs with heart failure [2]. The expected variability



**Figure 9**

Visual predictive check of PKPD model 10 for PAWP in patients with acute heart failure (symbols are observations, median is thick line, 90% prediction intervals are thin lines). Low (.....), median (—), high (.....), observed (○)

in response due to patient variability is illustrated in Figures 9 and 10. Based on this variability the percentage of patients in this study who would reach the target effect was 64% based on the loading dose and 62% based on the proposed maintenance dose rate.

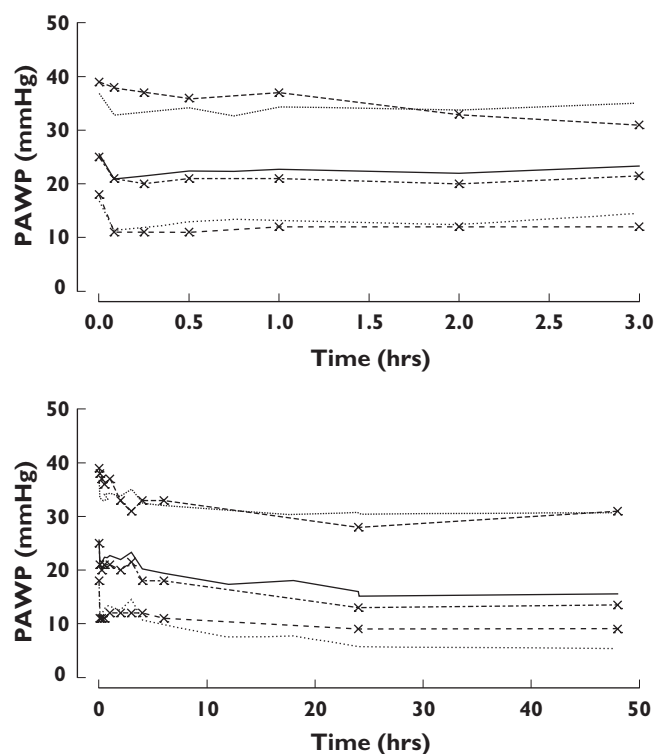
We could not detect any evidence of tachyphylaxis over the 48 h administration period. Larsen et. al. also reported that nicorandil did not induce tachyphylaxis [4], so there is reason to expect that nicorandil would continue to be effective if administered for longer periods.

We recommend that in patients with AHF, nicorandil be initially administered as a loading dose of  $200 \mu\text{g kg}^{-1}$  followed by an infusion of  $400 \mu\text{g kg}^{-1} \text{h}^{-1}$ . It is predicted that this regimen would lead to an average 30% reduction in PAWP. The subsequent infusion rate should be adjusted based upon clinical response.

*We thank Dr. Takeshi Kamijo for reviewing this manuscript.*

### Competing interests

Satofumi Iida and Haruki Kinoshita work at Chugai Pharmaceutical Co., Ltd and Dr Nicholas Holford has served as an outside consultant in their research.



**Figure 10**

Visual predictive check of PKPD model 10 in patients with acute heart failure for PAWP (lines with symbols are observations and without symbols are predictions; median is thick line, 90% prediction intervals are thin lines). Low (.....), median (—), high (.....), OBS low (----), OBS median (-----), OBS high (---)

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