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Pharmacokinetics of Procainamide and N-acetylprocainamide during Continuous Renal Replacement Therapy

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Abstract

Procainamide and its major metabolite, N-acetyl procainamide (NAPA), prolong the QTc interval and can promote potentially fatal ventricular arrhythmias. Excretion of procainamide and NAPA is reduced in patients with chronic kidney disease (CKD) resulting in drug accumulation and toxicity. The elimination of procainamide or NAPA in patients undergoing continuous renal replacement therapy (CRRT) has not been evaluated increasing the risk for subtherapeutic or toxic dosing regimens. This case report describes a patient undergoing CRRT who was administered procainamide for recurring ventricular tachycardia (VT) over approximately a 36 hour period. The patient required increased vasopressor therapy and developed QTc prolongation during procainamide administration. The VT resided following pacemaker adjustments, procainamide administration, and multiple direct current cardioversion attempts. Procainamide and NAPA concentrations were determined over a 120 hour period as part of routine clinical care and a pharmacokinetic (PK) model was developed using NONMEM. The developed PK model was used to simulate several procainamide dosing regimens to optimize therapy during CRRT. Based on the model-based simulations, a 50% reduction in the procainamide maintenance dose (2 mg/min) in CKD patients on CRRT can achieve therapeutic plasma procainamide and combined procainamide/NAPA concentrations.

Introduction

Procainamide is a Vaughan-Williams (VW) Class IA antiarrhythmic drug used for treatment of hemodynamically stable monomorphic ventricular tachycardia in patients with normal left ventricular function and atrial fibrillation in the setting of pre-excitation.¹ Procainamide elimination occurs through renal excretion, as well as hepatic acetylation to the major metabolite, N-acetyl procainamide (NAPA).² N-acetyl procainamide is also predominantly renally excreted and has a VW classification as a Class III antiarrhythmic drug.² Therefore, both procainamide and NAPA prolong the QT interval and can promote the potentially fatal ventricular arrhythmia, torsades de pointes, particularly at high concentrations (above 12 mg/L or 16 mg/L for procainamide and 30 mg/L for combined procainamide and NAPA concentrations).³⁻⁶

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Excretion of both procainamide and NAPA is significantly reduced in patients with chronic kidney disease (CKD) resulting in drug accumulation.⁷⁻⁹ Several studies have evaluated the efficiency of different renal replacement therapies in removal of both compounds in patients with diminished kidney function.¹⁰⁻¹² However, elimination in patients with CKD who are undergoing continuous renal replacement therapy (CRRT) has not been evaluated. This information could facilitate the appropriate procainamide dosing regimen for CRRT patients to optimize the time to reach therapeutic outcomes while decreasing the risk for torsades de pointes. This report describes the pharmacokinetics (PK) of both procainamide and NAPA in a CKD stage 5 patient undergoing CRRT. Additionally, simulations of procainamide and NAPA exposure following several dosing regimens are performed to help guide dosing in patients undergoing CRRT.

Case Report

A 40-year-old white male presented to Indiana University Health (IUH) Methodist Hospital in Indianapolis, Indiana with severe aortic valve stenosis. His past medical history included restrictive lung disease resulting from radiation therapy for Hodgkin's lymphoma, human immunodeficiency virus positive, hyperlipidemia, depression, history of cocaine abuse, hypertension, hypothyroidism, and CKD. The patient was transferred to the intensive care unit (ICU) following aortic valve replacement (AVR) and left brachiocephalic vein ligation. A temporary pacemaker was placed following the AVR. Prior to admission, the patient was undergoing hemodialysis on Mondays, Wednesdays, and Fridays (HD MWF) for CKD stage 5. His serum creatinine was 10 mg/dL upon admission to the ICU and the nephrology service was consulted. CRRT was initiated on his second hospital day and maintained at a rate of 2000 ml/hr for the entire ICU stay. CRRT was performed using PRISMA system (Hospal, Lyon, France). Hemofiltration was performed using the acrylonitrile (AN69) and sodium methallyl sulfonate (M100) hemofilter set. Blood flow rate was maintained at 150 ml/min. The patient did not require additional renal replacement therapy during his hospital admission.

The patient developed postoperative hypotension due to suspected cardiogenic shock and was treated with vasopressors and positive inotropic agents. The dosages of these drugs on postoperative day 2 included intravenous (IV) norepinephrine 30 µg/min, epinephrine 0.6 µg/kg/min, vasopressin 0.04 units/min and milrinone 0.5 µg/kg/min. On postoperative day 3, the patient developed an irregular wide complex tachycardia with intermittent signs of atrial flutter and fibrillation. The rhythm eventually became regular with QRS complexes that were consistent with monomorphic ventricular tachycardia (VT). The initial VT was converted to normal sinus rhythm with synchronized direct current cardioversion (DCC) (100 J × 6) and a procainamide loading dose of 1000 mg (50 mg/min IV for 20 min). Following the loading dose, procainamide was administered by a continuous IV infusion of 2 mg/min for 6 hours.

Three additional episodes of monomorphic VT occurred several hours later and were managed by three synchronized DCC procedures. Additionally, the maintenance dose of procainamide was increased to 4 mg/min due to persistent VT. The post-cardioverted patient remained in accelerated junctional rhythm. Upon reviewing telemetry ECG strips, each run of VT was preceded by a pacing spike on the T wave of an intrinsic beat. Therefore, the pacemaker sensitivity settings were changed to avoid misfiring and minimize this potential trigger of VT. Eight hours following the pacemaker setting adjustment, DCC, and increased procainamide dosing, the patient did not experience any additional episodes of VT. Therefore, the procainamide infusion rate was reduced to 2 mg/min for 7 hours and then to 1 mg/min for approximately 13 hours, at which time it was discontinued.

Vasopressor therapy was increased and continually adjusted throughout the course of procainamide administration as a result of the worsening hypotension. Over the entire course of therapy, the patient's systolic / diastolic blood pressure ranged from 86–130 / 40–60 mmHg. The patient had a baseline heart rate corrected QT interval using Bazett's formula (QTc) between 416 to 442 ms prior to AVR. During the initial infusion the QTc interval was elevated at 513 ms with a heart rate of 103 beats per minute (bpm) and remained elevated at 477 ms at the end of procainamide administration with a heart rate of 94 bpm. Serial blood samples were collected during procainamide therapy over a period of 120 hours due to the potential for drug accumulation and toxicity. The time course of samples obtained relative to procainamide dosing are presented in Figure 1. Plasma concentrations of procainamide and NAPA were determined by Syva Emit® Enzyme Immunoassay (Siemens Healthcare Diagnostics, NY, USA) run on the Beckman Coulter DxC 800 (Beckman Coulter, Inc., CA, USA) in the clinical laboratory at IUH Methodist Hospital. The patient was discharged from the ICU to long-term care 52 days after admission.

Pharmacokinetic Analysis

Plasma concentrations of procainamide and NAPA were used to develop a pharmacokinetic (PK) model that describes the drug and metabolite disposition during CRRT. Compartmental PK modeling was performed using NONMEM (Version VII; Globomax LLC, MD, USA).¹³ One- and two- compartment models were fit to the observed procainamide concentrations to determine the most appropriate model to describe procainamide PK. Appropriateness of the model to describe the observed data was determined using goodness-of-fit plots, change in objective function value, and agreement of estimated PK parameters with previous literature.^{14,15} A two-compartment open model with first order elimination from the central compartment was used to describe procainamide PK during CRRT. A third compartment was used to represent NAPA formation from procainamide followed by its elimination from the central compartment. All elimination, metabolic, and distribution processes were assumed to be first-order¹⁵ (equations 1–3).

$$\frac{dX(1)}{dt} = R_0 - \frac{Cl_{f,napa}}{(V_c)_P} \cdot X(1) - \frac{Cl_{other}}{(V_c)_P} \cdot X(1) - \frac{Cl_d}{(V_c)_P} \cdot X(1) + \frac{Cl_d}{(V_p)_P} \cdot X(2) \quad (1)$$

$$\frac{dX(2)}{dt} = \frac{Cl_d}{(V_c)_P} \cdot X(1) - \frac{Cl_d}{(V_p)_P} \cdot X(2) \quad (2)$$

$$\frac{dX(3)}{dt} = \frac{Cl_{f,napa}}{(V_c)_N} \cdot X(1) - \frac{Cl_{napa}}{(V_c)_N} \cdot X(3) \quad (3)$$

Where X(1), X(2), and X(3) are the amounts of procainamide in the central and peripheral compartments and the amount of NAPA in the central compartment, respectively; dX(1)/dt, dX(2)/dt, and dX(3)/dt are the rates of change of procainamide amount over time in central and peripheral compartments and the rate of change of NAPA amount over time in central compartment; (V_c)_P, (V_p)_P, and (V_c)_N are the procainamide apparent volumes of distribution in the central and peripheral compartments and the NAPA apparent volume of distribution in the central compartment, respectively; R₀ is the zero-order infusion rate; Cl_{f,napa} is the formation clearance of NAPA from procainamide, Cl_{other} combines all other procainamide clearance pathways (CRRT, renal, metabolic), Cl_d is procainamide distribution clearance, and Cl_{napa} is NAPA total clearance (CRRT and renal). Residual unexplained variability (RUV) was modeled using a proportional error term according to equation 4:

$$y_i = \hat{y}_i * (1 + \varepsilon_i) \quad (4)$$

Where y_i is the i^{th} observed concentration, \hat{y}_i is the i^{th} model-predicted concentration, and ε_i is the residual error term for the i^{th} observation.

The final model was able to adequately describe the plasma concentration-time profiles for both procainamide and NAPA as displayed in figure 1. The final model was able to estimate all of the PK parameters except for the NAPA volume of distribution due to lack of information on fraction of procainamide elimination that result in NAPA formation. This parameter was fixed based on reported values in the literature of NAPA disposition in functionally anephric patients on hemodialysis (approximately 1.5 L/kg).⁹ Based on this patient's weight (70 kg), $(V_c)_N$ was fixed to 100 L and all other parameters were successfully estimated. The estimated PK parameters from the final model are displayed in Table 1.

Simulation of Exposure after Different Dosing Regimens

The final PK model was used to simulate systemic exposure to procainamide, NAPA, and total exposure (procainamide + NAPA). The recommended IV infusion loading dose of procainamide is 20 mg/min for 25–30 min for patients with normal liver and kidney function. The recommended maintenance dose is 2–6 mg/min for patients without renal or hepatic dysfunction and a 25–50% reduction in this dose is recommended for patients with renal dysfunction.^{4,16} We simulated procainamide, NAPA, and total concentrations after a procainamide IV infusion loading dose of 20 mg/min for 30 min followed by IV maintenance doses of 4 mg/min (regular dose for normal kidney function), 2 mg/min (50% reduction), or 1 mg/min (75% reduction) given for 48 hours (Figure 2). The optimal dosing regimen for use in patients undergoing CRRT was chosen based on achievement of therapeutic and non-toxic procainamide and total concentrations. The target therapeutic ranges used in this evaluation were 4–12 mg/L and 10–30 mg/L for procainamide and combined procainamide/NAPA concentrations, respectively.⁴ A 50% reduction in regular maintenance dose achieved therapeutic and potentially non-toxic procainamide and total concentrations. Therefore, this dosing regimen may be the optimal dosing regimen to initiate in patients with CKD stage 5 undergoing CRRT.

Discussion

Several renal replacement therapies have been shown to remove procainamide and NAPA with variable efficacy. However, the relative capability of CRRT in the removal of procainamide and NAPA as compared to other extracorporeal techniques has not been assessed. Moreover, due to the lack of information on how procainamide is eliminated in patients on CRRT, the appropriate dose adjustment in such population is unknown. Data observed in this report enabled the evaluation of procainamide elimination by CRRT and simulation of different maintenance dosing rates.

It has been reported that hemoperfusion (HP) is more effective than hemodialysis (HD) in removal of both procainamide and NAPA, whereas peritoneal dialysis does not remove either compound effectively.¹⁰ Combined HD/HP has also been shown to be an effective technique for treatment of procainamide toxicity but the intermittent regimens can result in rebound increases in procainamide or NAPA plasma concentrations after the end of dialysis sessions as a result of their large volumes of distribution.¹² Continuous arteriovenous hemofiltration and hemodiafiltration are more effective than intermittent hemodialysis in reduction of toxic NAPA concentrations.¹¹

Exposure of procainamide and NAPA in a CKD stage 5 patient undergoing CRRT in this case report was adequately described by the developed PK model. The estimated procainamide clearance (Cl_{other}) that does not result in NAPA formation was 3.54 L/hr. This clearance estimate combines elimination through residual kidney function (1400 ml / 24 hrs in this patient), as well as CRRT. Procainamide clearance through CRRT could not be estimated separately from residual renal elimination due to lack of procainamide dialysate concentrations or availability of plasma concentrations while the patient was not on CRRT. Nonetheless, the estimated Cl_{other} is less than procainamide dialytic clearance reported for HD in previous studies (4–4.5 L/hr).^{7,15} However, the total (dialytic and non-dialytic) procainamide clearance estimated in the study by Atkinson and colleagues (approximately 8 L/hr) is similar to the estimated procainamide total clearance (Cl_{p}) in our study (7.2 L/hr).¹⁵ A similar procainamide clearance (approximately 7.2 L/hr) was also previously estimated using combined HD/HP in an anuric patient.¹²

Procainamide plasma concentrations were reduced to less than 1 mg/L by the end of the third day following termination of the infusion. Elimination of NAPA by CRRT and residual kidney function was similar to that of procainamide with an estimated clearance of 2.9 L/hr. Measurable NAPA concentrations (1.7 mg/L) were still observed on the fourth day following termination of procainamide infusion which might be explained by continuous formation of NAPA from procainamide. Estimated NAPA clearance (2.9 L/hr) is comparable to the reported clearance for HP (2.8 L/hr) and less than that reported for HD (4.6 L/hr) or combined HD/HP (7.8 L/hr).¹² However, CRRT displayed the advantage of overcoming rebound increase in plasma concentrations.

Model-based simulations using the estimated PK parameters in this case report showed that a 2 mg/min maintenance dose in patients on CRRT would immediately achieve therapeutic procainamide concentrations and achieve therapeutic combined procainamide/NAPA concentrations within approximately 8 hours (figure 2b). Continuation of this rate for 48 hours would maintain procainamide and combined procainamide/NAPA concentrations within the therapeutic ranges of 4–12 mg/L and 10–30 mg/L for about 24 and 48 hours post infusion, respectively.⁴ On the other hand, a 4 mg/min maintenance dose quickly achieves supra-therapeutic procainamide concentration within approximately 0.5 hours. Given the lack of information about the efficiency of CRRT in elimination of procainamide and NAPA, the reported patient was started on 2 mg/min for 6 hours before the dose was doubled and then decreased again after 8 more hours. Based on the simulated concentrations, the initial rate of 2 mg/min would have eventually achieved the therapeutic target with potentially a lower risk of hypotension or QTc interval prolongation.

In conclusion, CRRT effectively removes procainamide and NAPA similar to other renal replacement therapies in a patient with residual kidney function. Based on results of our model-based simulations, a 50% reduction in regular procainamide maintenance dose in CKD patients on CRRT can serve as a guide to achieve the recommended therapeutic plasma procainamide and combined procainamide/NAPA concentrations in patients with residual kidney function. Anuric patients on CRRT may require further dosage reduction and a 1 mg/min maintenance dose may reduce the potential for toxicity in such patients. Procainamide and NAPA concentrations should still be monitored in CKD patients on CRRT following the start of procainamide infusion.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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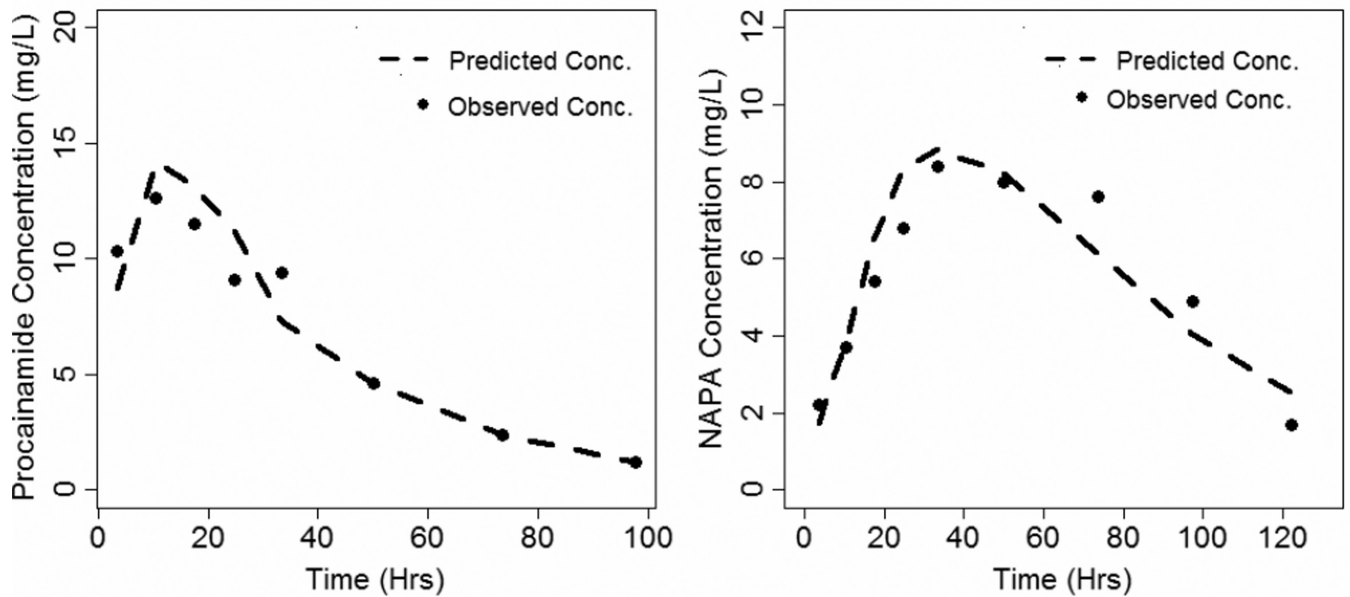


Figure 1.

Plasma concentration-time profiles for (A) procainamide and (B) NAPA following a procainamide loading dose of 1000 mg (17.5 mg/kg) administered by IV infusion at a rate of 50 mg/min for 20 min, followed by continuous IV infusions of 2mg/min for 6 hours, 4 mg/min for 8 hours, 2 mg/min for 7 hours, and 1 mg/min for approximately 13 hours in a single patient on CRRT. Solid circles represent the observed concentrations and the black dashed lines represent the model-predicted concentrations.

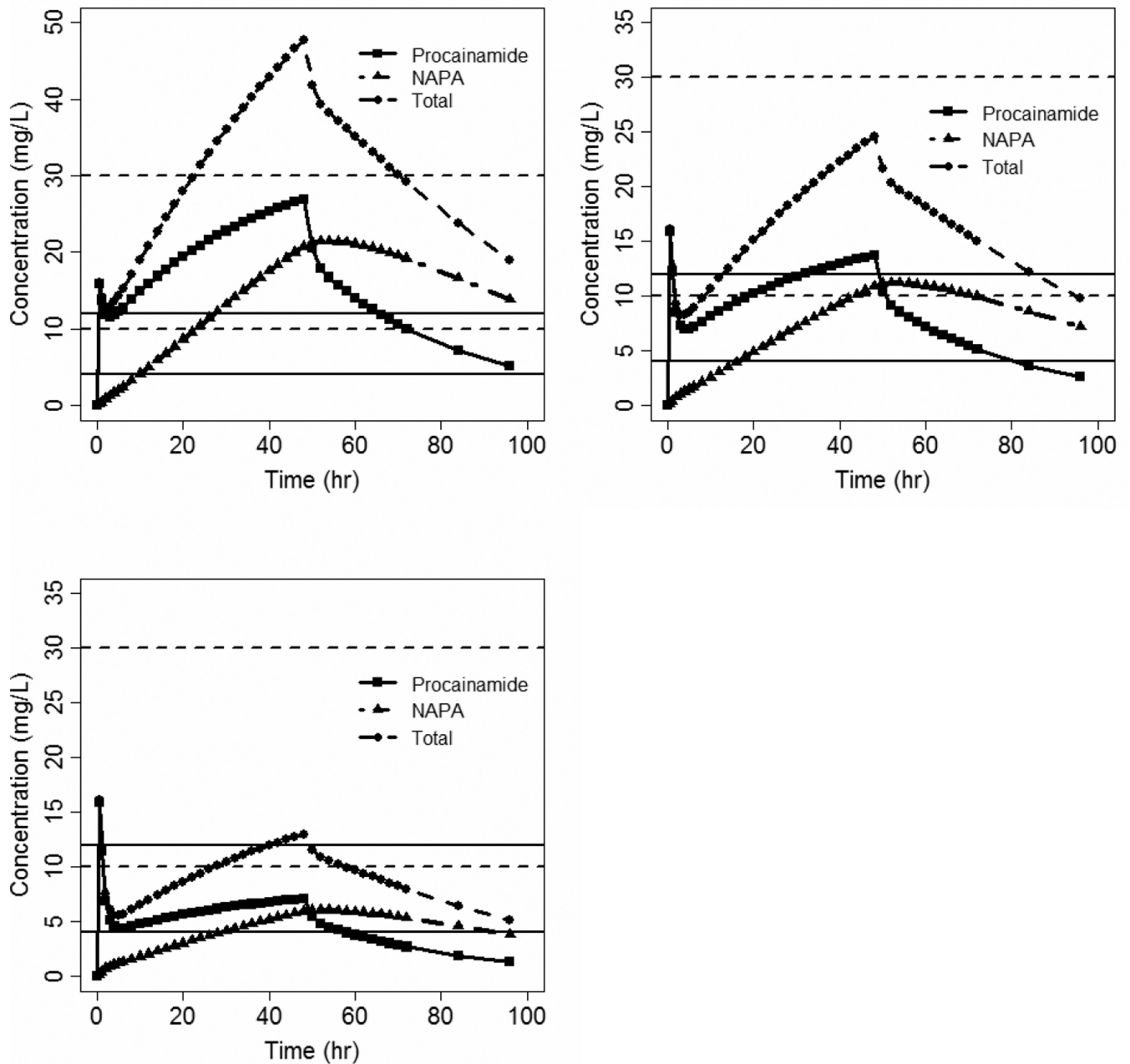


Figure 2. Simulated plasma concentration-time profiles after three different dosing regimens. A. Loading dose: 20 mg/min for 30 min, maintenance dose: 4 mg/min for 48 hrs. B. Loading dose: 20 mg/min for 30 min, maintenance dose: 2 mg/min for 48 hrs. C. Loading dose: 20 mg/min for 30 min, maintenance dose: 1 mg/min for 48 hrs. Closed squares and solid lines represent procainamide concentrations, closed triangles and dot-dashed lines represent NAPA concentrations, and closed circles and dashed lines represent total concentrations. The horizontal solid and dashed lines represent therapeutic ranges for procainamide and total concentrations, respectively.

Table 1

Estimated PK parameters (with relative standard errors of the estimates) using the final compartmental PK model.

PK parameter	Final Parameter Estimate	Relative Standard Error (%)
Cl _{other} (L/hr)	3.54	44.3
Cl _{f,napa} (L/hr)	3.70	26.3
Cl _{napa} (L/hr)	2.96	32.1
Cl _d (L/hr)	19.1	24.6
(V _c) _P (L)	30.7	82.5
(V _c) _N (L)	100 _(fixed)	NA
(V _p) _P (L)	169	26.9