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Pharmacokinetics of Procainamide and N-acetylprocainamide

In-Jin Chang*, Jae-Gook Shin*, Sang-Goo Shin*, Chan-Woong Park and Jung-Kyoo Lim
Department of Pharmacology, College of Medicine, Seoul National University
and Clinical Pharmacology Unit, Seoul National University Hospital*

ABSTRACT

To evaluate disposition characteristics of procainamide and its active metabolite, N-acetylprocainamide (NAPA), cross-over study for procainamide and NAPA was performed in 5 male adult dogs. After single administration of 10 mg/kg procainamide over 15 minutes, the range of measured plasma NAPA concentrations during experimental period were 0.03 to 0.124 ug/ml and early 'dip' phenomenon was distinct on NAPA concentration to time curve in all 5 dogs. Volume of distribution (Vss) and central compartment volume (Vc) of procainamide were 1.20±0.27 L/kg of body weight and 0.36±0.08 L/kg, respectively. Vss and Vc of NAPA were 1.21±0.21 L/kg and 0.26±0.07 L/kg, respectively. Intercompartmental clearance (Clint) of procainamide was 3.44 L/kg/hr and that of NAPA was 1.62 L/kg/hr. Total body clearance (Cl) of procainamide and NAPA were 0.47±0.08 and 0.35±0.08 L/kg/hr. The half-life ($t_{1/2\beta}$) of procainamide and NAPA were 2.85 hrs and 2.77 hrs, respectively.

Metabolic clearance (Clm)of procainamide by N-acetylation was 18.24±6.22 ml/kg/hr, which corresponded to 3.9% of total procainamide clearance.

Key Words: Procainamide, N-acetylprocainamide, pharmacokinetics, dogs.

INTRODUCTION

Mark *et al.* (1951) introduced procainamide as an effective antiarrhythmic agent from the wide screening for the derivatives and metabolites of procaine which had antiarrhythmic activity. Thereafter, procainamide has been in clinical use for the prevention or treatment of ventricular arrhythmia for more than 30 years. Currently, procainamide is widely used as an effective type 1 antiarrhythmic agent though its disadvatages such as short interval of drug administration and frequent serious adverse effect of systemic lupus-like syndrome with long-term use limit clinical use of this drug (Koch-Weser *et al.*, 1969; 1971; Giardina *et al.*, 1973; Weinstein, 1980; Uetnecht and Woosley, 1981).

The relationship between plasma level of procainamide and its effect has been established (Koch-Weser, 19747; 1977; Giardina *et al.*, 1973; Gey *et al.*, 1974), and many studies showed that great differences in administered dose for the optimum therapy without toxic side effect were found in different patients (Miller *et al.*, 1952; Patton *et al.*, 1969). Thus, adjustment of procainamide dose to individual patient has become an important feature in its clinical use.

After report by Dreyfuss *et al.*, (1972), in which N-acetylprocainamide (NAPA) was found as an active metabolite of procainamide in human, a number of papers introduced the antiarrhythmic effect of this metabolite in mice (Drayer *et al.*, 1974; Elson *et al.*, 1975), dogs and isolated dog Purkinje fibers (Drayer *et al.*, 1974; Bagwll *et al.*, 1974), guinea pig atrial strip (Karlsson *et al.*, 1975), and man (Elson *et al.*, 1975; Atkinson *et al.*, 1977; Kluger *et al.*, 1980). Appreciable plasma concentration of NAPA, an active metabolite of procainamide, was noticed after transient procainamide therapy (Giardina *et al.*, 1976). Contrary to the procainamide, 85% of administered NAPA was eliminated by kidney (Dutcher *et al.*, 1977), and hence accumulation of NAPA after adminintration of procainamide was prominent in the renal failure (Gibson *et al.*, 1977; Stec *et al.*, 1977). These results indicate that monitoring of

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plasma NAPA as well as procainamide concentration is recommended during procainamide therapy and dose regimen of procainamide must be adjusted by results of monitoring.

Our study was undertaken to analyze pharmacokinetic characteristics of these compounds and especially pharmacokinetic character in the metabolism of procainamide into NAPA. Cross-over study was taken for the procainamide and NAPA with 1 week interval in the dog.

METHODS

Five adult dogs (mean body weight; 11.5±1.7 kg) were studied for the procainamide and NAPA with the interval of 1 week. All animal were anesthetized by first administering sodium pentobarbital, 20 mg/kg, intravenously, followed by continuous infusion of maintenance dose 2 mg/kg/hr mixed with normal saline. An angiocatheter (18 G) with a heparin lock was placed within a femoral artery, connected to a perssure transducer, and permitted blood sampling and systemic blood pressure monitoring, another intravenous catheter (21 G) was inserted into a peripheral vein on foreleg for the infusion of normal saline or drug to maintain constant urine flow.

After obtaining control blood samples, procainamide HCl or NAPA HCl, 10 mg/kg of body weight, was infused with Sage infusion pump over a period of 15 minutes. Serial blood sampls were drawn at 5, 10, 15, 16, 18, 20, 25, 30, 40, 60, 90, 120, 180, 240, 300, 360 and 480 minutes through indwelled catheter placed within femoral artery. Blood samples were centrifuged to separate plasma immediately. Obtained plasma samples were stored at -20℃ for subsequent analysis.

Measurement of plasma procainamide and NAPA concentrations

Plasma samples and standard solutions were extracted before assay as follows; To 0.5 ml of plasma or standard solutions were added 0.5 ml of internal standard solution containing 5.0 ug/ml of p-nitro-N-(2-diethyl-aminoethylbenzamide), 0.1 ml of 2 N NaOH and 2.5 ml ethylacetate. After vortexing for 2 minutes and centrifugation (1000× G for 10 minutes), the organic layer was transferred to a dryness with rotary evaporator. The residue was dissolved in 100 ul of mobile phase and a 20 ul sample was injected for assay into HPLC column.

Chromatographic analysis was done by a modified method of Dutcher and Strong (1970), using Gilson model 302 pump, fixed UV-detector (Gilson) set at 254 nm with C-R-6A Chromatopac integrator (Shimatzu, Japan), six-port rotary valve injector (Model 7161, Rheodyne, Berkerldy co, USA) with 20 ul sample loop. The chromatographic separations were achieved using normal phase, Zorbax silica column (25 cm ×4.6 mm ID, 6um, Gilson USA) with methanol-water-morpholine (100:1:0.1, v/v) as a mobile phase. Solvent flow rate was 1.2 ml/min.

Under these conditions, retention times of internal standard, NAPA and procainamide were 7.8, 10.7 and 14.0 minutes, respectively (Fig. 1). A

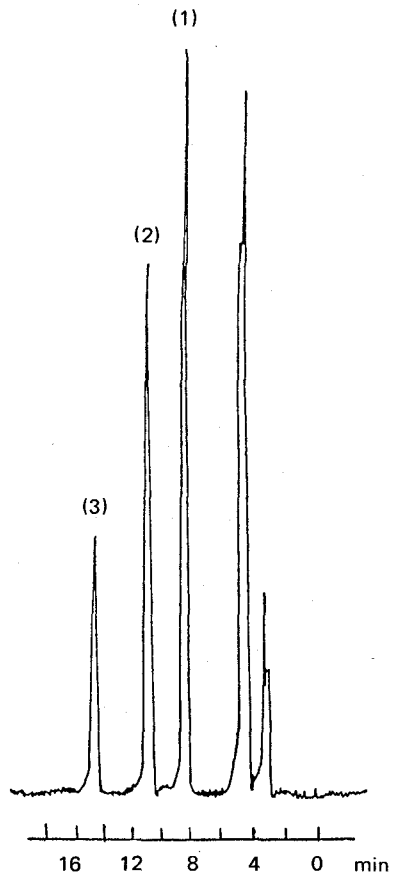

Fig. 1. Chromatogram of procainamide and its metabolite from plasma. 1=IS, p-nitro-N (2-diethyl-aminoethylbenzamide), 2=N-acetylprocainamide, 3=procainamide

plot of area ratio of procainamide and NAPA to internal standand were linear from 0.1 to 8 ug/ml (Fig. 2). Coefficient of variation of this method was estimated under 6.8%.

Pharmacokinetic analysis

Even though three-compartment model can be distinguished when procainamide or NAPA was infused intravenously at rapid rate (Strong *et al.*, 1975; Dutcher *et al.*, 1977; Stec and Atkinson, 1981), it is possible to define the parameters for only a two-compartment distribution model (Graffner *et al.*, 1974; Galeazzi *et al.*, 1976; 1981; Lima *et al.*, 1979) when administration of procainamide or NAPA is slower just as our experimental design. We used two-compartment model for the analysis of pharmacokinetic parameters of each drug.

Analysis of pharmacokinetic parameters of procainamide or NAPA was done by non-linear iterative fitting to minimize the sum of the squared deviations of the measured data points from the optimum theoretical plasma concentrations for the model parameters with computer program PCNONLIN (Metzler, 1986). The parameter of km, first order rate constant of N-acetylation from procainamide to NAPA, was estimated by non-linear regression of NAPA concentration data after administration of procainamide with previously obtained pharmacokinetic parameters of each drug.

Based on this model (Fig. 3), instantaneous rate of change of concentrations of drug in the central compartment of procainamide (dC_{1PA}/dt) and NAPA (dC_{1NP}/dt) is equal to;

$$V_{CPA} \cdot \frac{dC_{1PA}}{dt} = k_{12}X_{2PA} - (k_{12} + kr + km) \cdot X_{1PA}$$

$$V_{CNP} \cdot \frac{dC_{1NP}}{dt} = kmX_{1PA} + km_2X_{2NP} - (km_1 + kn) \cdot X_{1NP}$$

where, X indicate the amount of drug in each compartment. Laplace transformation of these differential equations were done to describe the time course of NAPA concentration of central compartment after intravenous infusion of procainamide.

The terminal half-life ($t_{1/2\,\beta}$) of procainamide

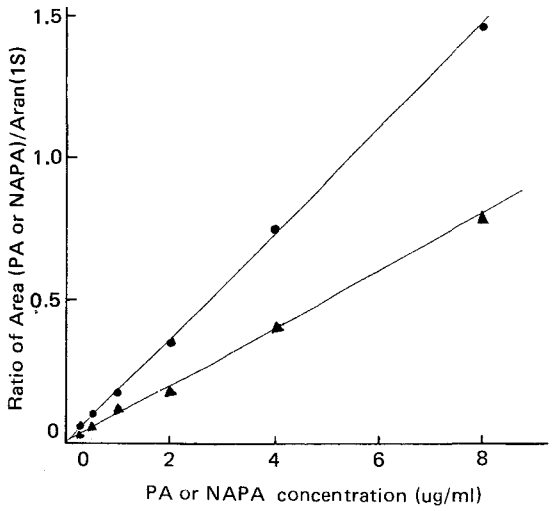

Fig. 2 Standard curve for the Procainamide (▲) or NAPA (●) concentration to the ratio of area (Procainamide or NAPA)/area (Internal standard, p-nitro-N-(2-diethyl-aminoethyl-benzamide).

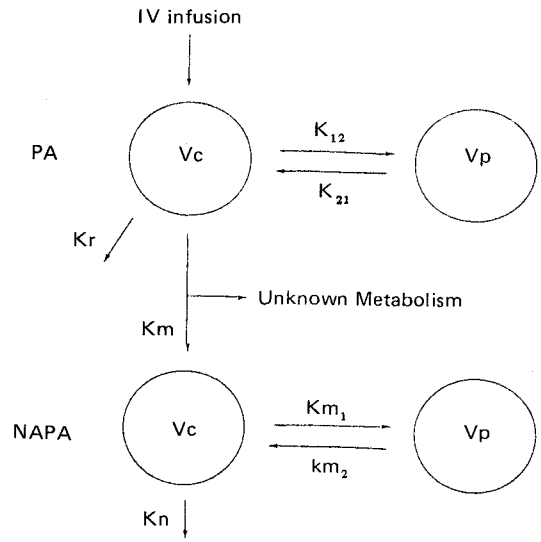

Fig. 3 Pharmacokinetic model used to analyze the pharmacokinetics of procainamide (PA) and N-acetylprocainamide (NAPA) distribution, metabolism and elimination. Abbreviations used are: Vc, central compartment volume; Vp, peripheral compartment volume; k_{12}, k_{21}, k_{m1}, k_{m2}, intercompartmental transfer rate constant; V_{1m}, elimination rate constant of PA by N-acetylation; k_r, renal elimination rate constant of PA; k_n, elimination rate constant of NAPA by renal and nonrenal route.

and NAPA elimination was calculated from the following equation;

$$t_{1/2\,\beta}=0.693/\beta$$

Intercompartmental clarances (Clint) were obtained from the product of volume of distribution and appropriate intercompartmental transfer rate constant according to the equation (Perrier and Gibaldi, 1974):

$$Clint=k_{12}\cdot Vc=k_{21}\cdot Vp$$

Elimination clearances were calculated from the product of Vc and elimination rate constant by;

$$Cl=k_{10}\cdot Vc$$

RESULTS

Pharmacokinetic parameters of procainamide and NAPA in 5 dogs are given in Table 1. Volume of distribution at steady state (Vss) and central compartment volume (Vc) of procainamide were 1.20±0.27 L/kg and 0.36±0.08 L/kg. Peripheral compartment volume (Vp) was larger than central compartment and was about 70% of $Vssp_A$. Similar results of Vss and Vc were observed in NAPA, in which Vp was 78.5% of Vss_{NP}.

Intercompartmental clearance (Clint) was 3.44 L/kg/hr for procainamide and 1.6 L/kg/hr for NAPA. This result indicates more rapid tissue distributon of procaimanide than that of NAPA. Total body clerance (Cl) of procainamide was 0.47±0.08 L/kg/hr, which was greater than that of NAPA, 0.35±0.08 L/kg/hr. N-acetylation of procainamide to NAPA attributed to the 3.9% of total body clearance. The $t_1/_{2\,\beta}$ of procainamide and NAPA were 2.85 and 2.75 hours, respectively, which were significantly shorter than those of other reports in human study.

After single infusion of procainamide and NAPA over 15 mimutes, plasma concentration time curve showed biphasic decay (Fig. 4). Peak plasma concentrations at 15 minutes of procainamide and NAPA were 10.8 and 22.3 ug/ml in dog 2 shown in fig. 4, respctively. The range of formed NAPA concentration was 0.03 to 0.124 ug/ml during experimental period after single administration of procainamide 10 mg/kg (Fig. 4A). NAPA concentration-time curve after a single procainamide dose showed "early dip phenomenon" by tissue distribution of formed NAPA. This results are found in all 5 dogs.

DISCUSSION

Estimated volume of distribution (Vss) was

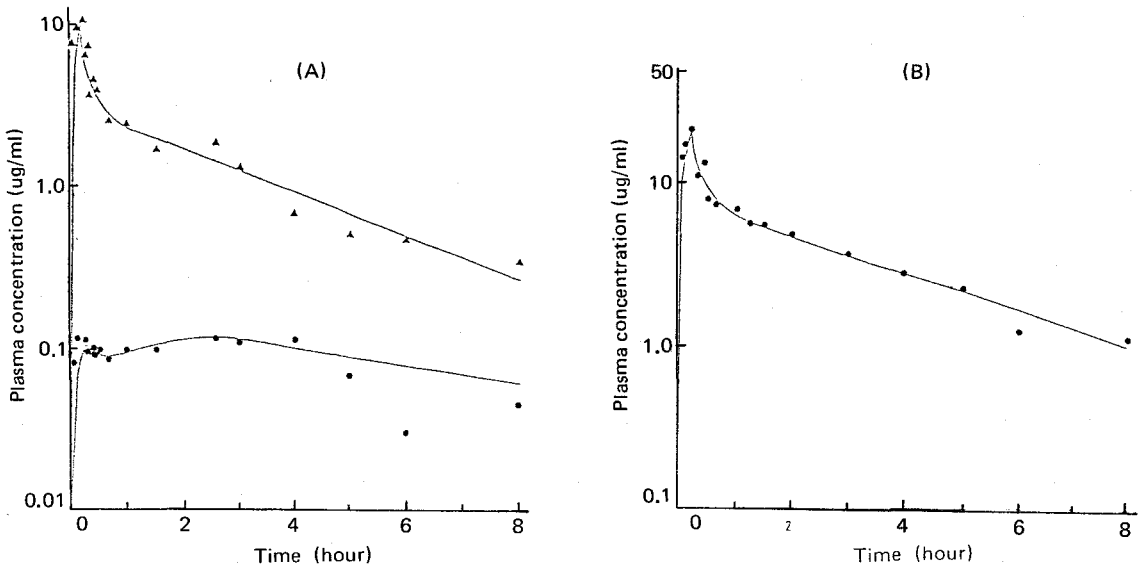

Fig. 4 Representative plasma procainamide (▲) and N-acetylprocainamide (●) concentration to time profile after single administration of 10 mg/kg procainamide to dog 2, (A) Representative plasma N-acetylprocainamide concentration to time profile after single administration of 10 mg/kg N-acetylprocainamide to dog 2, (B). The solid lines represent the lines of least-squares fit of the data points.

Table 1. Pharmacokinetics of procainamide and its metabolite, NAPA in dog

No.	Procainamide					NAPA					Clm (ml/kg/hr)
	Vc_{PA} (L/kg)	Vss_{PA} (L/kg)	$Clint_{PA}$ (L/kg/hr)	Cl_{PA} (L/kg/hr)	$t_{1/2PA}$ (hrs)	Vc_{NP} (L/kg)	Vss_{NP} (L/kg)	$Clint_{NP}$ (L/kg/hr)	Cl_{NP} (L/kg/hr)	$t_{1/2NP}$ (hrs)	
1	0.28	1.62	3.53	0.42	2.92	0.31	1.20	1.21	0.36	2.69	8.36
2	0.46	2.27	3.31	0.39	2.18	0.16	0.85	1.76	0.28	2.35	23.67
3	0.37	1.95	4.0	0.47	3.10	0.27	1.31	1.61	0.32	3.20	15.98
4	0.29	1.89	3.11	0.59	2.54	0.24	1.29	1.81	0.30	3.36	21.87
5	0.41	2.25	3.27	0.49	3.50	0.34	1.39	1.69	0.48	2.24	21.32
Mean	0.36	1.20	3.44	0.47	2.85	0.26	1.21	1.62	0.35	2.77	18.24
±S.D.	0.08	0.27	0.35	0.08	0.51	0.07	0.21	0.24	0.08	0.05	6.22

Abbreviations: Vc, central compartment volume; Vss, steady-state volume of distribution; Clint, intercompartmental clearance; Cl, total body clearance; $t_{1/2}$, terminal half-life; Clm, metabolic clearance of procainamide by N-aectylation.

similar in procainamide and NAPA in dog (Table 1), which suggests similar distribution of these drugs in the body. This results are similar with values (2.0±0.42 L/kg) previously reported by others who studies in human (Dutcher *et al.*, 1977; Manion *et al.*, 1977; Lima *et al.*, 1979; Galeazzi *et al.*, 1976), and suggest that there would be no significant difference in distribution patterns of procainamide and NAPA between dog and human. Peripheral compartment volumes (Vp) of procainamide and NAPA were 70% and 78.5%, which seems that larger portion of administered procainamide and NAPA in the body was distributed in deep tissue. Intercompartmental clearance of procainamide was larger than that of NAPA, which agrees with the report of Gibson et al. (1977). Total body clearance and the $t_{1/2\beta}$ of NAPA in dog were significantly greater and shorter than those in human (Dutcher *et al.*, 1977).

The "early dip phenomenon" of plasma NAPA concentration-time curve was found in all 5 dogs after single IV infusion of procainamide for 15 minutes (Fig. 4A). Following statements may explain this phenomenon: a) NAPA is formed in the central compartment (Litterst *et al.*, 1975); b) concentration of NAPA formed decreases due to rapid distribution into larger peripheral compartment at non-equilibrium state.

Metabolism was attributed to 46.0±6.8% of total body clearance of procainamide in normal human (Dutcher *et al.*, 1977; Gibson *et al.*, 1983), and N-acetylation of arylamine group by N-acetyltransferase was known as a major metatolic pathway of procainamide (Reidenberg *et al.*, 1975; Hein *et al.*, 1982). A number of reports for elimination of procainamide administered were introduced (Graffner *et al.*, 1975; Elson *et al.*, 1975; Gibson *et al.*, 1975; Karlsson *et al.*, 1974), and Giardina *et al.* (1976) reportd that 7 to 24% (15±1.8) of administered procainamide dose was excreted in the urine as a form of NAPA during first 24 hours in 5 normal and 5 patients with heart disease after single oral administration of 7 to 13 mg/kg dose of procainamide. In our study, procainamide clearance by N-acetylation corresponded to 3.9% of the total body clearance in dog (Table 1), and maximun cncentration of NAPA in plasma was 0.15±0.08 ug/ml in 5 dogs after single IV infusion of 10 mg/kg dose of procainamide. This result suggests that metabolic pathway of N-acetylation of procainamide is not so important in dog compared to human and the mechanism for shorter half-life of procainamide in dog than in human seems mainly due to greater renal clearance, not shown in this experiment.

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= 국문초록 =

Procainamide와 그 대사산물(N-acetylprocainamide)의 약동학적 분석에 관한 연구

서울대학교 의과대학 약리학교실 및 서울대학교병원 임상약리학 Unit*

장인진* · 신재국* · 신상구* · 박찬웅 · 임정규

Procainamide를 투여후 이 약물 및 활성형 대사산물인 N-acetylprocainamide (NAPA)의 약동학적 성상을 알아보기 위해 숫컷 성견 5마리에 procainamide 및 NAPA를 교차 투여하여 얻은 혈장농도 data를 2-compartmental model에 의해 약동학적 분석을 시행하여 다음과 같은 결과를 얻었다.

1. 10 mg/kg의 procainamide를 1회 15분간 정주후 혈장 procainamide 농도변화는 명백한 분포기와 소실기를 보였으며 생성된 NAPA의 혈장농도는 시간경과에 따라 최고혈장농도는 0.124 μg/ml 이하이었으며 정주 직후 조직분포에 따른 혈장농도의 일시적으로 감소 후 증가하는 초기 dip 현상을 보였다.

2. Procainamide의 steady-state 분포용적(Vss) 및 central compartment volume (Vc)은 각각 1.20±0.27 L/kg 및 0.36±0.08 L/kg 이였으며 NAPA의 Vss 및 Vd는 1.21±0.21 L/kg 및 0.26±0.07 L/kg이었다.

3. Procainamide 및 NAPA의 청소율(Cl)은 각 0.47±0.08 L/kg/hr와 0.35±0.08 L/kg/hr 이었으며 혈장 반감기($t_{1/2\beta}$)는 각각 2.85 및 2.77 시간이었다.

4. N-acetylation에 의한 Procainamide의 대사청소율은 18.24±6.22 ml/kg/hr로 이는 전체 procainamide 청소율의 3.9%를 차지하였다.