J. Reddy Kambam MD, R.J. Naukam BS,
B.V.R. Sastry PHD

The effect of procainamide on plasma cholinesterase activity

The in vitro effect of procainamide on plasma cholinesterase (PChE) activity in the plasma of ten normal ASA physical status I patients was studied using a kinetic method. The mean plasma cholinesterase activity without procainamide (control) was 0.90 ± 0.09 units·ml⁻¹. The dibucaine numbers of all the samples were in the normal range of 78 to 86, indicating normal genotypes. The mean plasma cholinesterase activity, in the presence of procainamide in concentrations of 5.0, 10.0, 20.0 and 40.0 µg·ml⁻¹, was reduced to 0.73 ± 0.04 , 0.61 ± 0.03 , 0.45 ± 0.02 , and 0.36 ± 0.01 units·ml⁻¹, respectively. At therapeutic concentrations of 4 to 12 µg·ml⁻¹, procainamide inhibited cholinesterase activity 15 to 30 per cent. The authors also showed that the concentration of procainamide required to inhibit 50 per cent of plasma cholinesterase activity was 20 µg·ml⁻¹ (I₅₀). The authors conclude that procainamide when tested in vitro had a statistically significant depressant effect on plasma cholinesterase activity at all the concentrations studied.

The interaction between procainamide, a potent antiarrhythmic drug, and both depolarizing and nondepolarizing muscle relaxants has been documented in the sciatic nerve-tibialis anterior muscle preparation of the anaesthetized cat.¹ Procainamide is known to inhibit the release of acetylcholine at the neuromuscular junction and thus prolongs the duration of action of nondepolarizing muscle relaxants.² However, the mechanism for the interaction between procainamide and succinylcholine, a depolarizing muscle relaxant has not been elucidated. Intravenous infusion of procainamide hydrochloride in a dose range of 2 to 20 mg·kg⁻¹ had shown to have no neuromuscular blocking effect in the absence of muscle relaxants.¹

Key words

ENZYMES: plasma cholinesterase; HEART,
ANTIARRHYTHMICS: procainamide.

From the Departments of Anesthesiology (JRK) and Pharmacology (RJN, BVR), Vanderbilt University Medical Center, Nashville, Tennessee.

Address correspondence to: Dr. J. Reddy Kambam, Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, Tennessee 37232.

Procaine, an ester type of local anaesthetic, is also known to potentiate the action of succinylcholine both in humans and in animals.^{3,4} Since procaine and succinylcholine are hydrolyzed by the same plasma cholinesterase enzyme, this potentiation of succinylcholine action was thought to be due to the substrate competition.⁴ To our knowledge, the effect of procainamide on plasma cholinesterase activity has not been reported. Therefore, we studied the effect of procainamide on pseudocholinesterase in the plasma of ten healthy ASA physical status I patients.

Methods

With the prior approval of our Institutional Review Board for the Protection of Human Subjects, informed consent was obtained from ten healthy ASA physical status I patients (both sexes, aged 18–28). Ten ml of venous blood was collected into a heparinized syringe from each patient. Plasma was immediately separated for the determination of cholinesterase activity and dibucaine numbers (DN). A kinetic method described by Zapf *et al.* utilizing naphthyl acetate substrate was used in the determination of plasma cholinesterase activity and dibucaine numbers.⁵ All the values reported were the average means of duplicate determinations of plasma cholinesterase activity.

The reaction mixture contained 1-naphthyl acetate as substrate in phosphate buffer with a pH of 7.50. The total volume of the reaction mixture was 3 ml. Procainamide was added *in vitro* to the reaction mixture to give a final concentration of 5.0, 10.0, 20.0 and 40.0 µg·ml⁻¹. After determining a baseline absorbance at 321 nm in a Beckman Model 24 recording spectrophotometer, the reaction was started with the addition of 100 µl of plasma sample. The absorbance change was recorded and cholinesterase activity was expressed as units per ml of plasma. One unit corresponds to the liberation of 1 micromole of 1-naphthol per minute under the conditions of assay.

Linear regression analyses and correlation coefficients were calculated between log procainamide concentrations and PChE activities. Correlation coefficients (*r*) with corresponding *p* < 0.01 were considered significant. In addition to regression analyses, analysis of variance and Dunnett's test were used to compare the drug effects against the control.

TABLE I Effect of procainamide on plasma cholinesterase activity (PCHE)

Concentration of procainamide ($\mu\text{g}\cdot\text{ml}^{-1}$)	PCHE (units $\cdot\text{ml}^{-1}$)	% Inhibition from control
0 (control)	0.90 ± 0.09	—
5	$0.73 \pm 0.04^*$	19
10	$0.61 \pm 0.03^*$	32
20	$0.45 \pm 0.02^*$	50
40	$0.36 \pm 0.01^*$	60

*Significantly different from control, $p < 0.01$ (Dunnett's test).

Results

Results are shown in Table I. The mean plasma cholinesterase activity of the control plasma samples was $0.90 \text{ units}\cdot\text{ml}^{-1}$. When procainamide was added to the reaction mixture to get a concentration of 5.0, 10.0, 20.0 and $40.0 \mu\text{g}\cdot\text{ml}^{-1}$, the mean plasma cholinesterase activity was reduced to 0.73, 0.61, 0.45 and $0.36 \text{ units}\cdot\text{ml}^{-1}$, respectively. Dibucaine numbers of all the plasma samples were in the normal range of 78 to 86. There was a significant correlation between log concentrations of procainamide versus PCHE activity ($r = 0.99$, $p < 0.001$) (Table II).

The figure shows a plot of per cent inhibition of PCHE activity against log plasma procainamide concentrations. The concentration of procainamide required to inhibit 50 per cent of PCHE activity (I_{50}) was found to be $20 \mu\text{g}\cdot\text{ml}^{-1}$.

Discussion

Procainamide is an effective pharmacological agent used in the treatment of premature ventricular contractions and recurrent ventricular tachycardia.⁶ Procainamide is also useful in the treatment of ventricular dysrhythmias occur-

TABLE II Regression analyses for plasma cholinesterase activity versus log procainamide concentrations

Plasma sample	Slope	Intercept	Correlation coefficient (r)	p
1	-0.355	0.951	-0.99	<0.001
2	-0.372	0.978	-0.99	<0.001
3	-0.405	1.001	-0.99	<0.001
4	-0.452	1.039	-0.99	<0.001
5	-0.395	0.967	-0.99	<0.001
6	-0.412	0.999	-0.99	<0.001
7	-0.455	1.101	-0.99	<0.001
8	-0.457	1.119	-0.99	<0.001
9	-0.472	1.123	-0.99	<0.001
10	-0.405	0.986	-0.99	<0.001
Mean	-0.418	1.026	-0.99	<0.001
SD	0.039	0.065	—	—

FIGURE Effect of procainamide on plasma cholinesterase (PCHE) activity ($I_{50} = 20 \mu\text{g}\cdot\text{ml}^{-1}$).

ring in patients with malignant hyperpyrexia.⁷ The therapeutic concentration of procainamide is considered as 4 to $12 \mu\text{g}\cdot\text{ml}^{-1}$.⁸

Plasma cholinesterase is a mucoprotein produced in the liver which is responsible for the metabolism of succinylcholine, a depolarizing muscle relaxant and all the ester type of local anesthetics. Plasma cholinesterase has no documented physiological importance.

Several drugs are known to inhibit PCHE activity.^{9,10} PCHE is also depressed in pregnant patients and in patients with significant hepatic dysfunction.^{11,12} Investigators have shown that there is a correlation between PCHE activity and the duration of paralysis produced by a single dose administration of succinylcholine.¹³ However, the correlatory effect between PCHE activity and the recovery of muscle twitch from the administration of multiple doses of succinylcholine has not been studied. The depressant effect of procainamide on PCHE activity may not be clinically significant in healthy patients with normal levels of PCHE activity. However, in patients with moderate decrease in PCHE activity as seen in pregnant patients and in patients with significant hepatic dysfunction, a further decrease in PCHE activity up to 30 per cent caused by procainamide could become clinically significant. Systemic toxicity caused by ester type local anaesthetics has been documented in patients with significant decrease in PCHE activity.¹⁴

In conclusion, we demonstrated that procainamide when tested *in vitro* has a statistically significant inhibitory effect on plasma cholinesterase activity ($p < 0.01$). Our data also showed that the concentration of procainamide required to inhibit 50 per cent of the plasma cholinesterase activity is $20 \mu\text{g}\cdot\text{ml}^{-1}$.

terase activity is $20 \mu\text{g}\cdot\text{ml}^{-1}$. We recommend that neuromuscular paralysis should be monitored with a peripheral nerve stimulator in patients receiving procainamide and muscle relaxants.

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Résumé

On a étudié l'effet in vitro de la procainamide sur l'activité de la cholinestérase plasmatique (PCHE) dans le plasma de dix patients normaux de statut physique ASA I, à l'aide d'une méthode cynétique. L'activité de la cholinestérase plasmatique moyenne sans procainamide (groupe témoin) était de 0.90 ± 0.09 unités $\cdot\text{ml}^{-1}$. Les nombres de dibucaine, pour tous les échantillons, se situaient dans l'échelle normale de 78 à 86 dénotant, de ce fait, des génotypes normaux. La présence de procainamide dans des concentrations de 5.0, 10.0, 20.0 et $40.0 \mu\text{g}\cdot\text{ml}^{-1}$, réduisait l'activité de la cholinestérase plasmatique moyenne à 0.73 ± 0.04 , 0.61 ± 0.03 , 0.45 ± 0.02 , et 0.36 ± 0.01 unités $\cdot\text{ml}^{-1}$, respectivement. Des concentrations thérapeutiques de 4 à $12 \mu\text{g}\cdot\text{ml}^{-1}$ de procainamide inhibaient l'activité de la cholinestérase de 15 à 30 pour cent. Les auteurs ont aussi démontré que la concentration de procainamide requise pour inhiber 50 pour cent de l'activité de la cholinestérase plasmatique était de $20 \mu\text{g}\cdot\text{ml}^{-1}$ (I_{50}). Les auteurs concluent que la procainamide testée in vitro a un effet dépressif statistiquement significatif sur l'activité de la cholinestérase plasmatique à toutes les concentrations étudiées.