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Effects of *N*-Acetylprocainamide and Procainamide on Myocardial Contractile Force, Heart Rate, and Blood Pressure (40547)[1]

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N-Acetylprocainamide (NAPA) is a major metabolite of procainamide (PA) (1). Previous work in our laboratory has suggested that NAPA may be as potent as PA in the prevention of ventricular fibrillation induced by chloroform in mice, and also in the treatment of premature ventricular contractions in patients (2).

Previous *in vitro* studies have shown that NAPA has positive chronotropic and inotropic effects in isolated rat atria (3). Clinical studies have also raised the possibility that NAPA has a positive inotropic effect, since the ratio of preejection period/left ventricular ejection time was reduced during NAPA therapy (4). On the other hand, these studies also suggested that NAPA has a negative chronotropic effect in patients, since sinus rate was significantly reduced.

Because the Walton–Brodie strain gauge arch (W–B gauge) (5) has been used previously to demonstrate the negative inotropic effect of PA (6, 7), we selected this gauge for studies in dogs to compare the effects of NAPA and PA on myocardial contractile force. Simultaneous observations were also made of the effects of both drugs on heart rate and systemic arterial pressure.

Materials and Methods. Surgical preparation. Eleven male mongrel dogs (18–25 kg) were anesthetized with pentobarbital sodium (30 mg/kg iv). After a tracheostomy, the dogs were ventilated with room air using a Harvard respirator (Model 607). Carotid blood pressure was measured with a Bell & Howell pressure transducer (type 4-327-0010). The right external jugular vein was cannulated for drug administration and continuous infusion of isotonic saline.

A right lateral thoracotomy was then performed to expose the heart. After bilateral vagotomy, cardiac contractile force was measured with a W–B gauge sutured to the right ventricle as described previously (8). Sutures were placed 1.5 cm apart and the feet of the gauge were separated by a 2.2- to 2.3-cm distance so that the segment of ventricular muscle was stretched to 150% of its initial length, as recommended by Cotten (9), and in order to avoid significant influence from changes in preload.

The electrocardiogram and heart rate were monitored with a cardiotachometer. Recordings of all parameters were made with a Beckman Model R611 Dynograph recorder. All baseline observations were stable for at least 10 min before initiation of the study.

Drug administration. *N*-Acetylprocainamide–HCl (Arnar-Stone Laboratories, Lot No. 160-35, 100 mg NAPA–HCl, 6.15 mg sodium acetate per ml) and procainamide–HCl (Squibb Laboratories, PA–HCl 100 mg, 0.9% benzyl alcohol and 0.09% sodium bisulfite per ml) were both administered by rapid intravenous injection. Initial screening of NAPA at doses of 1.25, 2.5, and 5.0 mg/kg in one dog indicated no effects on myocardial force, heart rate, or blood pressure. Thus, the dose range of 10 to 40 mg/kg was selected for study. Six dogs received 10, 20, and 40 mg/kg doses of NAPA, and then a series of equal doses of PA. Doses of both drugs were separated by an 8- to 10-min interval. Before NAPA administration, the preparations were checked for adequacy of positive inotropic response with norepinephrine bitartrate (NE) in doses of 0.062 and 0.125 μg/kg or 0.062, 0.125, and 0.25 μg/kg, depending on the re-

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sponse of each preparation. The first PA dose was given 15 to 20 min after the last NAPA dose. Prior to PA administration, the high dose of NE (0.125 or 0.25 μg/kg) was again administered as a positive control.

In order to determine if the sequence of administration influenced the responses to PA, three dogs were treated with this drug alone, in doses of 10, 20, and 40 mg/kg, and these results compared with those obtained with PA given after NAPA, as described above.

To assess the response to diluent administration, control studies were made in two dogs. NAPA diluent was a 0.615% solution of sodium acetate in 0.9% saline. PA diluent was 0.9% benzyl alcohol and 0.09% sodium bisulfite in 0.9% saline. Both diluents were given iv to each animal in doses of 0.1, 0.2, and 0.4 ml/kg, so that the amounts given would equal those received when the NAPA and PA solutions were injected. These control studies were preceded by the injection of a 0.4 ml/kg test dose of normal saline.

Data analysis. Parameter response was measured at peak effect and was expressed as percentage change compared with values recorded just before administration of each drug dose. The only exception was heart rate. Percentage changes in this parameter was compared with control values obtained just before the first dose of NAPA or PA. Mean arterial pressure was calculated as diastolic pressure plus one-third pulse pressure. The results are reported as mean ± SE. The effects of NAPA and PA administration were compared using two-tailed paired t tests with α set at $P = 0.05$. The effects of PA given alone and PA given after NAPA were compared with two-tailed t tests for two means, also with α set at $P = 0.05$.

Results. Myocardial contractile force. NAPA increased myocardial contractile force, particularly at the 40 mg/kg dose level (Table I, Fig. 1). PA, on the other hand, exerted a negative inotropic effect that appeared to be equivalent at all dose levels (Table I, Fig. 1). These responses were different from those observed with NAPA at all dose levels ($P < 0.01$ for the 10 mg/kg dose, and $P < 0.001$ for the 20 and 40 mg/kg doses).

There was no difference when PA was given alone or after NAPA, with respect to the negative inotropic effect ($P > 0.20$) (Table II). Neither the NAPA nor the PA diluents had any effect on myocardial force.

Adequacy of inotropic response was tested with NE, as described under Methods. The low dose of NE (0.062 or 0.125 μg/kg) elicited a +14.5 ± 3.5% change in myocardial force whereas the high dose (0.125 or 0.25 μg/kg) elicited a +33.7 ± 8.7% change. Repeat administration of the high dose of NE after NAPA treatment and before the first dose of PA, elicited a +29.2 ± 6.3% change in myocardial force. The latter was not different when compared to the initial high-dose administration of NE ($P > 0.20$).

Heart rate. NAPA consistently decreased heart rate in the six dogs studied (Table I), at all dose levels. PA induced similar changes in heart rate (Table I). However, the sequence of drug administration seemed to affect the magnitude of the negative chronotropic response after PA, since this effect was greater in the dogs given PA alone ($P < 0.05$, $P > 0.10$, $P < 0.02$ for the 10, 20, and 40 mg/kg doses, respectively) (Table II).

Three dogs had periods of apparent junc-

TABLE I. COMPARISON OF THE ACTIONS OF *N*-ACETYLPROCAINAMIDE AND PROCAINAMIDE ON MYOCARDIAL FORCE, HEART RATE AND BLOOD PRESSURE IN DOGS.

	Dose		
	10 mg/kg	20 mg/kg	40 mg/kg
Myocardial force[a]			
NAPA ($n = 6$)	+5.0 ±3.3	+6.5 ±3.7	+21.8 ±5.6
PA ($n = 6$)	−13.7 ±2.5[b]	−16.8 ±2.1[c]	−12.7 ±3.5[c]
Heart rate[a]			
NAPA ($n = 6$)	−12.0 ±0.9	−19.2 ±1.2	−23.7 ±1.7
PA ($n = 6$)	−8.7 ±1.9	−14.5 ±2.5	−19.3 ±3.6
Mean arterial pressure[a]			
NAPA ($n = 6$)	−13.5 ±2.2	−18.8 ±3.4	−21.8 ±5.4
PA ($n = 6$)	−19.2 ±3.8[d]	−24.3 ±4.2[e]	−26.5 ±4.6[e]

[a] Results are expressed as percentage change from control value (mean ± SE).
[b] $P < 0.01$ compared with NAPA.
[c] $P < 0.001$ compared with NAPA.
[d] $P > 0.05$ compared with NAPA.
[e] $P > 0.20$ compared with NAPA.

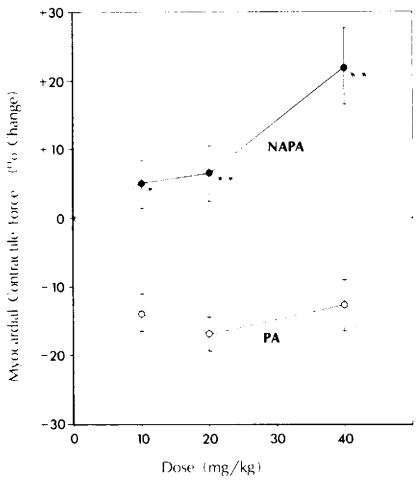

FIG. 1. The effects of *N*-acetylprocainamide (NAPA) and procainamide (PA) on myocardial force of contraction. A Walton–Brodie strain gauge was sutured to the right ventricular wall in six vagotomized dogs under pentobarbital anesthesia. NAPA and PA were given by rapid iv injection, with a 10-min interval between doses, and a 20-min interval between NAPA and PA treatment. Results are expressed as percentage change (mean ± SE) compared with control values (indicated by the dotted line). (*) $P < 0.01$ (paired t test) compared with PA. (**) $P < 0.001$ (paired t test) compared with PA.

tional tachycardia after the 20 or 40 mg/kg NAPA doses, and the 10 or 20 mg/kg doses of PA. Heart rate went from a baseline of 150 to 166 beats per minute to 166 to 200 beats per minute during the arrhythmia.

Neither the NAPA nor the PA diluents affected heart rate in the control studies.

Blood pressure. NAPA caused a reduction in mean blood pressure at all doses (Table I). Maximal effects followed soon after iv injection, and were more pronounced for diastolic than for systolic blood pressure. PA also caused hypotension although the fall in blood pressure tended to be more sustained than after NAPA injection (Table I). No difference was demonstrated when PA was given alone or after NAPA ($P > 0.20$) (Table II). Similarly, there were no differences when the hypotensive effects of NAPA and PA were compared ($P > 0.05$ for the 10 mg/kg dose, $P > 0.20$ for the 20 and 40 mg/kg doses (Table I).

The diluents for NAPA and PA only minimally affected blood pressure. In fact, the NAPA diluent caused a minor increase in mean blood pressure in the control studies.

Discussion. This study was designed to compare the effects of NAPA and PA on myocardial contractile force. Previous studies in isolated rat atria (3) and in human subjects (4, 10) have suggested that NAPA may have a positive inotropic effect. However, the positive inotropic effects observed in rat atria were modest and occurred in conjunction with an increase in atrial rate that could at least partially account for this effect (11). The clinical observations were based on noninvasive determination of systolic time intervals, and hence, might be affected by the peripheral vascular effects of NAPA. In fact, it has been shown recently that the efficacy of NAPA in reducing the preejection period to left ventricular ejection time ratio in patients treated chronically with this drug, appears to be dependent on underlying myocardial functional state (12). If NAPA were to have positive inotropic effects, this would contrast markedly with the myocardial depressant actions of PA. Thus, it seemed of paramount importance to compare the inotropic effects of these two closely related drugs.

TABLE II. EFFECTS OF THE SEQUENCE OF DRUG ADMINISTRATION ON THE ACTIONS OF PROCAINAMIDE ON MYOCARDIAL FORCE, HEART RATE, AND BLOOD PRESSURE IN DOGS.

	Dose		
	10 mg/kg	20 mg/kg	40 mg/kg
Myocardial force[a]			
PA-1 ($n = 3$)[b]	−13.0 ±7.1	−17.7 ±13.9	−26.7 ±17.7
PA-2 ($n = 6$)[b]	−13.7 ±2.5[c]	−16.8 ±2.1[c]	−12.7 ±3.5[c]
Heart rate[a]			
PA-1 ($n = 3$)	−18.7 ±3.5	−22.7 ±5.8	−39.3 ±4.3
PA-2 ($n = 6$)	−8.7 ±1.9[d]	−14.5 ±2.5[e]	−19.3 ±3.6[f]
Mean arterial pressure[a]			
PA-1 ($n = 3$)	−13.7 ±5.4	−18.7 ±4.6	−26.7 ±3.5
PA-2 ($n = 6$)	−19.2 ±3.8[c]	−24.3 ±4.2[c]	−26.5 ±4.6[c]

[a] Results are expressed as percentage change from control values (mean ± SE).

[b] PA-1 indicates procainamide given alone, PA-2 indicates procainamide given after NAPA.

[c] $P > 0.20$ compared with PA-1.

[d] $P < 0.05$ compared with PA-1.

[e] $P > 0.10$ compared with PA-1.

[f] $P < 0.02$ compared with PA-1.

Our results confirm the myocardial depressant actions of rapidly administered iv PA, as measured with the W–B gauge in anesthetized, open-chest dogs. Since we only administered PA by iv bolus injections in doses of 10 to 40 mg/kg, we cannot compare out results to those of Austen and Moran (7), who found an increase in myocardial force of contraction with slow infusion of PA in doses smaller than 10 mg/kg. However, the same authors found that PA induced myocardial depression when given rapidly to dogs in doses as low as 0.5 mg/kg (7).

On the other hand, NAPA increased myocardial contractile force, most markedly at the 40 mg/kg dose level, and did not cause myocardial depression over the dose range investigated. Although we did not control heart rate by pacing, we measured inotropic changes in the face of a decrease in heart rate and excluded periods of junctional tachycardia. For this reason, the increase in myocardial force that we observed with NAPA cannot be attributed to an increased heart rate (13). Since the actions of NAPA on myocardial force could be indirect (i.e., catecholamine mediated), further studies are required to investigate this possibility. Preliminary results in our laboratory indicate that hexamethonium does not block the actions of NAPA on myocardial force, suggesting that the positive inotropic effects are not mediated by sympathetic reflexes. It is not clear to what extent the negative chronotropic effects of PA contributed to the negative inotropic response that was observed when this drug was administered.

Since our observations on heart rate were made in bilaterally vagotomized dogs, the negative chronotropic effects of NAPA and PA probably represent a direct action on the sinoatrial node. This action has been previously described for procainamide (14), and Amlie *et al.* have recently reported similar actions for both PA and NAPA in nonvagotomized dogs (15). The relatively greater effect of PA on heart rate when given alone compared with PA given after NAPA, suggests that both drugs may be acting at the same site to reduce heart rate. The reduction in heart rate could also be explained by an interference with sympathetic drive to the heart. The reason for the NAPA and PA-induced junctional tachycardia in some dogs remains to be elucidated.

Administration of either NAPA or PA was followed by a fall in mean arterial pressure. However, PA seemed to reduce systolic pressure to a greater extent than NAPA, in agreement with a recent report (15). This difference may be accounted for by the increase in myocardial force induced by NAPA. PA appears to reduce blood pressure, not only by depressing myocardial force of contraction, but by reducing peripheral vascular resistance through ganglionic blockade (16). The mechanism of NAPA-induced hypotension remains to be established.

These observations in dogs are of clinical significance since the iv formulation of NAPA that we have used is being evaluated currently in patients. Although the iv administration of NAPA may not carry the same risk of myocardial depression that is associated with rapid PA injection, the fact that both agents share peripheral vascular effects that may result in potentially dangerous hypotension warrants equal caution in their iv administration to patients.

Summary. The effects of *N*-acetylprocainamide (NAPA) and procainamide (PA) on myocardial force of contraction were compared in open-chest, vagotomized, pentobarbital-anesthetized dogs, with the use of a Walton–Brodie strain gauge sutured to the right ventricle. NAPA increased myocardial force of contraction, particularly at the high dose level (40 mg/kg). PA, on the other hand, had a negative inotropic effect that was equally apparent at all doses (10–40 mg/kg). In addition, both NAPA and PA had a negative chronotropic effect and caused a reduction in mean arterial pressure. The mechanisms of the inotropic and hypotensive actions of NAPA require elucidation. Some of the implications of these findings for the clinical use of NAPA as an antiarrhythmic agent are discussed.

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