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The Hemodynamic Actions of *N*-Acetylprocainamide in Dogs: Kinetics of Effects and Plasma Concentration–Response Relationships[1] (40835)

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N-Acetylprocainamide (NAPA) is the major metabolite of procainamide (PA) in man (1). NAPA has antiarrhythmic efficacy and may be as potent as PA (2). Evidence is accummulating that differences between these related drugs may be clinically beneficial. Recent work from our laboratory suggests that NAPA is less likely than PA to cause a drug-induced lupus syndrome (3, 4). NAPA's elimination is slower and more predictably related to creatinine clearance, allowing for more convenient dosing intervals and better dosage individualization than is possible for PA (5–8). Finally, the hemodynamic effects of NAPA and PA appear to differ. In dogs, NAPA and PA share hypotensive and negative chronotropic actions, but NAPA increases myocardial contractile force whereas PA has negative inotropic effects (9).

These properties make it likely that NAPA will be useful as an antiarrhythmic drug in its own right. Therefore, this study was undertaken in dogs to provide a detailed analysis of NAPA's hemodynamic effects. Particular emphasis has been directed to analyzing the time course of these effects during the intravenous infusion of NAPA and to elucidating the plasma concentration–response relationships of this drug.

Materials and methods. Surgical procedures. Thirteen mongrel dogs, weighing 18.2 to 25.0 kg, were anesthetized with chloralose 100 mg/kg and urethane 500 mg/kg, intravenously. Chloralose–urethane anesthesia was chosen for these experiments because this anesthetic mixture preserves cardiovascular reflex mechanisms (10, 11). A tracheostomy was performed and the animals were ventilated with a Harvard pump using room air. The right carotid artery was cannulated for intraarterial blood pressure monitoring (Statham P23Db transducer), and the left external jugular vein was cannulated for blood sampling. The right femoral vein was cannulated to administer saline intravenously throughout the experiment (0.2 ml/kg/min) and to infuse NAPA or control diluent according to the experimental protocol.

The chest was opened through a sternotomy and the pericardium incised to expose the heart, aortic root, and the pulmonary artery. After dissection of fat and adventitial tissue, an electromagnetic flow probe (Narco Biosystems) was placed around the aorta to record cardiac output continuously with a Narco RT-500 flowmeter. A plastic cannula was then inserted through the left ventricular apex to monitor left ventricular end diastolic pressure (LVEDP) with a Statham P23Db transducer. A Walton–Brodie strain gauge (W-B gauge) was subsequently sutured to the wall of the right ventricle as described previously (9), to measure myocardial force of contraction. The W-B gauge was sutured to the right ventricle considering that changes in pulmonic impedance do not consistently affect right MCF and to isolate measurements of myocardial contractile force from changes in systemic impedance (afterload) (12). The segment of the right ventricular muscle sutured to the gauge was stretched to 150% of its initial length to minimize the effects of changes in preload, as recommended by Cotten and Bay (12).

In those dogs identified as the NAPA paced group (see below), cardiac pacing was accomplished by placing two aligator clamps on the right atrial appendage (bipo-

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lar pacemaker). Heart rate was monitored continuously in all dogs with a cardiotachometer (Grass Model 7P4) that could be switched to display the electrocardiogram at selected intervals in order to check cardiac rhythm and artificial pacemaker capture when appropriate. All recordings were made with a Grass Model 7 polygraph recorder, with the exception of LVEDP. This parameter was displayed on a storage oscilloscope, and photographic records were made at specified intervals.

Hemodynamic parameters. Systemic arterial pressure, LVEDP, heart rate (HR), cardiac output (CO), and myocardial contractile force (MCF) were measured as described above. Mean arterial pressure (MAP) was calculated as diastolic pressure plus 1/3 pulse pressure. Total peripheral vascular resistance (TPR) was calculated as the ratio of MAP in mmHg to CO in liters per minute, and expressed in arbitrary resistance units. Stroke volume (SV) was calculated as CO in ml/min divided by HR.

Drug administration. *N*-Acetylprocainamide as the hydrochloride salt (Arnar–Stone Laboratories Lot 160-35, NAPA–HCl 100 mg/ml, sodium acetate 6.15 mg/ml) was given by intravenous infusion with a Sage pump over 15 min. The administered dose of NAPA was 60 mg/kg. Control dogs received an infusion of NAPA diluent (sodium acetate, 6.15 mg/ml) using the same procedure. The volume of infusate was kept constant at 19 ml for all dogs by adding normal saline (0.9% NaCl) as necessary.

Experimental design. Dogs were divided into three groups: Four dogs receiving a NAPA diluent infusion (control group), five dogs receiving a NAPA infusion (NAPA nonpaced group), and four dogs receiving a NAPA infusion with cardiac pacing at a rate of 160–166 beats per minute (NAPA paced group). These rates of pacing were not significantly different from the baseline heart rates in the unpaced groups (Table I).

Once the surgical procedures were completed (approximately 2 hr after the initial dose of chloralose and urethane), one-half of the initial anesthetic dose was given by slow intravenous infusion over 10–15 min (chloralose 50 mg/kg, urethane 250 mg/kg). Parameter recording was begun 30–45 min after administering this second anesthetic dose because the dogs were hemodynamically stable by this time, as expected from previous reports (11). Measurements were made −3, −2, −1, 0, 2, 4, 5, 6, 8, 10, 12, 14, 15, 16, 17, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 50, 60, 75, 90, 105, and 120 min from the beginning of the NAPA or diluent infusions. Baseline values for each dog were calculated as the mean of values from −3 to 0 min.

NAPA plasma concentrations. Venous blood samples (5 cc) were obtained at 0, 5, 10, 15, 17, 20, 25, 30, 40, 50, 60, 75, 90, 105, and 120 min from the beginning of NAPA infusion. NAPA was measured by high-pressure liquid chromatography (13). No trace of PA was observed, indicating that NAPA was not deacetylated to PA during the time course of the experiment. Blood was drawn in the same volumes and at the same intervals in the control dogs.

Pharmacokinetic analysis. NAPA plasma concentration versus time curves

TABLE I. BASELINE HEMODYNAMIC PARAMETERS[a]

Parameter	Control $n = 4$	NAPA $n = 5$	NAPA paced $n = 4$
LVEDP (mmHg)	8.4 ± 3.2	3.0 ± 2.1	2.5 ± 1.7
MAP (mmHg)	137.5 ± 2.6	134.0 ± 5.6	123.4 ± 2.3
CO (liter/min)	1.9 ± 0.5	1.2 ± 0.2	2.1 ± 0.6
SV (ml)	11.9 ± 3.5	7.0 ± 1.1	13.2 ± 3.8
HR (beats/min)	163.7 ± 13.5	161.6 ± 9.7	161.5 ± 1.5
TPR (units)	84.4 ± 32.3	133.6 ± 24.1	69.7 ± 14.7

[a] All values are mean ± SE. Between groups there were no significant differences. NAPA = *N*-acetylprocainamide, LVEDP = left ventricular end diastolic pressure, MAP = mean arterial pressure, CO = cardiac output, SV = stroke volume, HR = heart rate, TPR = total peripheral resistance.

were generated for each dog by analyzing NAPA plasma concentrations with the SAAM 23 digital computer program developed by Berman and Weiss (14), implemented on a Model 6600 Control Data Corporation computer. The kinetics of NAPA distribution and elimination were modeled with the same three-compartment mamillary system used for pharmacokinetic studies in man (6). The computer iteratively adjusted the parameters of the model to minimize the sum of squared deviations between the computer-estimated plasma level versus time curves and the data. The respective mean deviation for the NAPA paced dogs was 1.63% and for the NAPA nonpaced dogs 2.09%. For each dog, the model was then used to provide plasma NAPA concentration estimates at the times that hemodynamic measurements were made.

Plasma concentration–response curves. These curves were constructed by selecting and averaging effects at approximately equal NAPA concentrations on the ascending and descending portions of the mean plasma concentration versus time curve for each group. Curves were then plotted as log-concentration:response relationships.

Data analysis. Results were expressed as percentage change compared with preinfusion values for each dog in all groups (control, NAPA nonpaced, and NAPA paced). The only exception was LVEDP and this parameter was expressed in mmHg change compared to preinfusion values. All results were reported as the mean ± SE. Means were compared using a two-tailed t test for 2 means, with $\alpha = 0.05$. Linear regression and correlation analyses were made with standard techniques (15).

Results. Baseline hemodynamic parameters are shown in Table I for the three experimental groups. There were no significant differences between the groups for any of the baseline parameters.

Plasma concentration–time curves. The mean plasma concentration–time curves resulting from NAPA infusion are shown in Fig. 1A. NAPA concentration increased rapidly during infusion to a 15-min peak of 158 ± 6.9 μg/ml (NAPA nonpaced) and 143 ± 8.9 μg/ml (NAPA paced). The plasma concentration subsequently decreased in a triexponential fashion, and by 120 min NAPA concentrations were 28.3 ± 1.8 μg/ml (NAPA nonpaced) and 26.7 ± 1.6 μg/ml (NAPA paced).

Myocardial contractile force. Significant increases in contractile force occurred immediately and were present for approximately 20 min in both treated groups compared to controls ($P < 0.05$) (Fig. 1B). Peak effects occurred at 8 min in the NAPA-nonpaced and NAPA-paced dogs (33.5 ± 7.5 and 31.6 ± 3.3%, respectively). In control dogs, MCF was stable for 50 min, but declined gradually thereafter, resulting in a 10.4 ± 5.7% decrease by 120 min. This decline was also present in both treated groups.

Mean arterial pressure. NAPA rapidly lowered MAP in all treated dogs (Fig. 1C). The time to peak effect was similar in the NAPA-nonpaced (26.5 ± 7.1% at 18 min) and NAPA-paced animals (33.5 ± 5.3% at 15 min). However, the duration of significant hypotensive effect ($P < 0.05$ compared to controls) was less in the NAPA-nonpaced than the NAPA-paced dogs (28 versus 75 min). After 75 min, no significant differences existed between all groups.

Total peripheral resistance. High NAPA concentrations decreased TPR. In control dogs, TPR was consistently elevated above baseline values throughout the study (Fig. 2A). A similar increase occurred in all groups after 50 min when NAPA plasma concentrations were less than 45 μg/ml. However, when NAPA plasma levels were higher than this, TPR was significantly decreased when compared to control dogs ($P < 0.05$). This effect was of longer duration in NAPA-paced than in NAPA-nonpaced dogs (50 versus 32 min). Peak reductions in TPR were also more pronounced in NAPA-paced dogs (29.1 ± 11.8 versus 15.0 ± 3.7%).

Linear regression and correlation analysis of the change in TPR (units) versus initial TPR were performed in both NAPA-nonpaced and NAPA-paced dogs. The change in TPR (resistance units) was estimated from the initial resistance and the lowest resistance observed during the

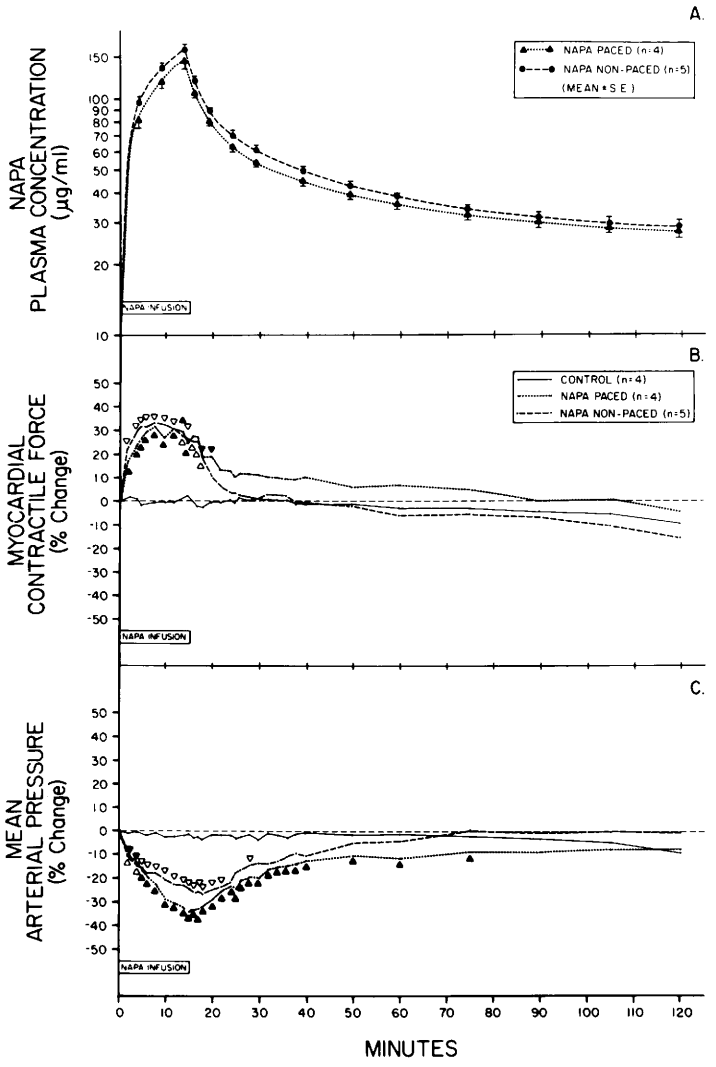

FIG. 1. (A) Plasma concentration versus time curve after a 60 mg/kg infusion of *N*-acetylprocainamide (NAPA) over 15 min in nonpaced and cardiac-paced dogs. (B) The time course of the increase in myocardial contractile force (MCF) in NAPA-nonpaced and NAPA-paced dogs. (C) Time course of the decrease in mean arterial pressure (MAP) in NAPA-nonpaced and NAPA-paced dogs. MCF and MAP results are expressed as percentage change from baseline in each group. Open triangles (△) indicate significant differences from controls ($P < 0.05$) in NAPA-nonpaced dogs. Closed triangles (▲) indicate significant differences from controls ($P < 0.05$) in NAPA-paced dogs.

NAPA infusion in each dog. There was a significant positive correlation between initial TPR and the maximal change observed during drug infusion in the NAPA-nonpaced group ($r = 0.94$, $P < 0.01$) (Fig. 3). No such correlation was observed in the NAPA-paced group ($r = 0.04$, $P > 0.05$).

Cardiac output. In both control and NAPA-nonpaced dogs, CO declined from baseline values, then stabilized at 20 min (Fig. 2C). In NAPA-paced dogs, CO was elevated above both baseline and control values for the first 6 min ($P < 0.05$), but subsequently declined to baseline, remaining significantly higher than control values ($P < 0.05$) from 22 to 40 min. After 50 min,

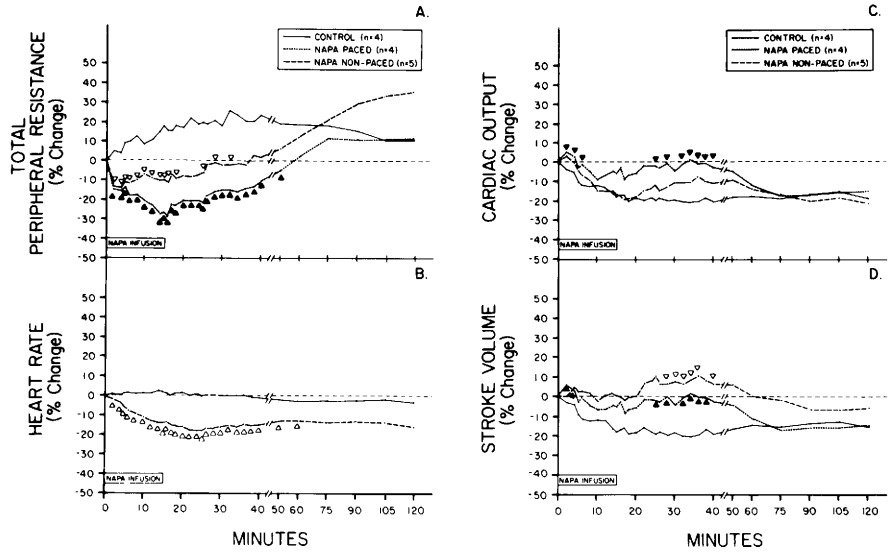

FIG. 2. Time course of effects of *N*-acetylprocainamide (NAPA) on: (A) total peripheral resistance, (B) heart rate, (C) cardiac output, and (D) stroke volume. Results are expressed as percentage change from baseline in each group. Open triangles (△) indicate significant differences from controls ($P < 0.05$) in NAPA-nonpaced dogs. Closed triangles (▲) indicate significant differences from controls ($P < 0.05$) in NAPA-paced dogs.

when plasma NAPA levels had fallen below 45 μg/ml, CO was similar in all experimental groups.

Heart rate. Significant decreases ($P < 0.05$) in HR occurred in the NAPA-nonpaced dogs when compared to controls for the first 60 min, when plasma NAPA levels were above 40 μg/ml (Fig. 2B). This effect was greatest at 24 min (18.5 ± 3.2%).

Stroke volume. SV declined from baseline values, reaching a plateau after 15 min in control dogs (Fig. 2D), but from 25 to 40 min was maintained above control values in both NAPA-nonpaced and NAPA-paced dogs ($P < 0.05$). In nonpaced dogs, SV was increased above baseline values during this period. The early increase in SV in NAPA-paced dogs (0 to 4 min) was also significantly different from controls ($P < 0.05$).

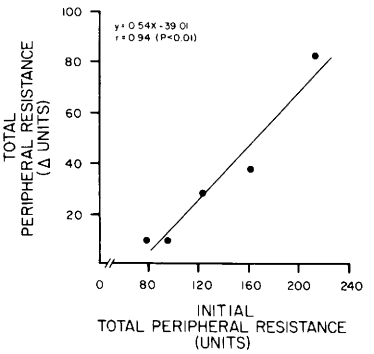

FIG. 3. Relationship between initial total peripheral resistance and maximal observed change in total peripheral resistance during *N*-acetylprocainamide (NAPA) infusion in NAPA-nonpaced dogs.

Left ventricular end diastolic pressure. No significant changes in LVEDP could be demonstrated in NAPA-treated dogs when compared to controls. In NAPA-nonpaced dogs mean LVEDP ranged −0.7 ± 2.3 to +2.7 ± 0.7 mmHg from baseline and only three points were significantly different from controls (8, 10, and 50 min, $P < 0.05$). In NAPA-paced dogs, LVEDP ranged −2.5 ± 1.3 to +2.2 ± 3.4 mmHg from baseline and differences also were insignificant.

Plasma concentration–response curves. Plasma concentration–response curves were constructed for MCF, HR, MAP, and TPR (see Methods). Responses were measured over the NAPA plasma concentration range of 52.9 ± 1.6 to 157.4 ± 4.7 μg/ml in NAPA-nonpaced dogs and 46.3 ± 2.1 to 140.7 ± 5.8 μg/ml in NAPA-paced dogs.

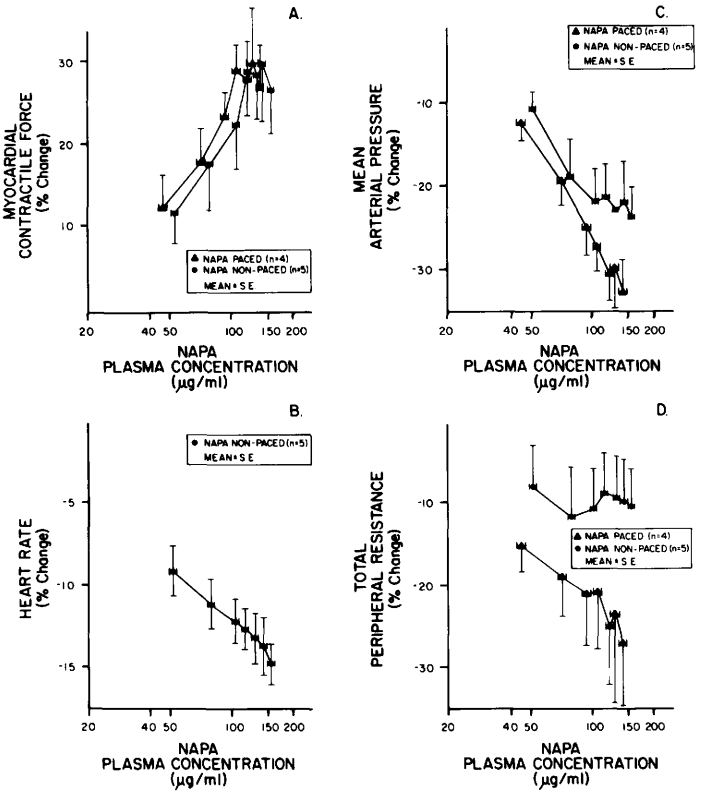

FIG. 4. *N*-Acetylprocainamide (NAPA) plasma concentration–response relationships in nonpaced and paced dogs. Curves are plotted as log-concentration versus effect (percentage change from baseline). (A) Myocardial contractile force (MCF). NAPA plasma concentration-related increase in MCF. (B) Heart rate (HR). NAPA plasma concentration related HR decrease in nonpaced dogs. (C) Mean arterial pressure (MAP). NAPA plasma concentration-related decrease in MAP. (D) Total peripheral resistance (TPR). NAPA plasma concentration-related decrease in TPR. The response in nonpaced dogs was of lesser magnitude and seemed triphasic.

(*a*) *Myocardial contractile force.* There was a log-linear relationship between increased MCF and NAPA concentration in both groups (Fig. 4A). An apparent effect plateau was reached at NAPA concentrations of 100 μg/ml in both groups.

(*b*) *Heart rate.* A log-linear relationship was observed between decreasing HR and NAPA concentration in the NAPA-nonpaced group. No plateau in response was apparent in the range of plasma concentrations studied (Fig. 4B).

(*c*) *Mean arterial pressure.* There was a log-linear relationship between MAP reduction and NAPA concentration for both NAPA-nonpaced and NAPA-paced groups (Fig. 4C). An apparent plateau was reached at NAPA concentrations of about 100 μg/ml in the NAPA-nonpaced group. No such plateau occurred in the NAPA-paced group over the range of plasma concentrations studies (Fig. 4C).

(*d*) *Total peripheral resistance.* The relationship between TPR reduction and NAPA plasma concentration was log-linear for the NAPA-paced group (Fig. 4D). No plateau was apparent over the range of plasma concentrations that was studied. The same trend was seen in the NAPA-nonpaced group, but the pattern appeared to be triphasic. TPR initially decreased with concentrations up to 80 μg/ml, but returned toward baseline values as NAPA plasma concentrations increased to 115 μg/ml. TPR

then fell as NAPA plasma concentrations rose to a maximum of 160 μg/ml.

Discussion. Although closely related in structure, NAPA and PA differ in their hemodynamic actions. Procainamide (PA) has marked hypotensive, negative chronotropic, and myocardial depressant actions (9, 16, 17). In the pentobarbital-anesthetized, bilaterally vagotomized dog, NAPA and PA caused similar reductions of HR and BP, but in contrast to PA, NAPA increased MCF (9).

The present study confirms our previous report that NAPA increases MCF as measured with the W-B gauge (9) and established that this positive inotropic effect correlated well with NAPA plasma concentration in the 50–100 μg/ml range, but appeared to plateau at higher concentrations. However, the increase in MCF peaked at 8 min, 7 min before peak NAPA plasma concentrations were reached. Since this effect was declining before NAPA plasma concentrations were maximal, it is possible that the positive inotropic effect of NAPA is indirect and mediated by a substance having different kinetics than NAPA (e.g., catecholamine release). Further studies are needed to establish the mechanism of this action. NAPA had similar positive inotropic effects in paced and nonpaced dogs, indicating that the negative chronotropic action of NAPA did not influence its enhancement of MCF in the range of heart rates encountered (e.g., on the basis of the force-frequency relationship) (18, 19).

NAPA had a consistent, plasma concentration-related negative chronotropic effect. However, HR was not maximally slowed until 8–10 min after the completion of the NAPA infusion. HR returned toward baseline only partially, and was still significantly different from control dogs at 60 min. These effects on HR were of longer duration than the effects on MCF (20 min), MAP (28 min), and TPR (32 min) in NAPA nonpaced dogs, but did parallel the duration of MAP and TPR reduction in the NAPA-paced dogs (75 and 50 min, respectively). We have previously shown that the same negative chronotropic effect is seen in bilaterally vagotomized dogs (9), suggesting a direct effect at the sinoatrial node. Amlie *et al.* (20) have also observed a reduction in HR with NAPA administration to non-vagotomized dogs, and Atkinson *et al.* (21) have described a reduced sinus rate in patients treated with NAPA for premature ventricular contractions.

NAPA infusion resulted in significant BP reductions in both the NAPA-nonpaced and NAPA-paced groups. These changes were plasma concentration related, and the course of effect followed NAPA plasma concentrations closely during and after the infusion of drug. The effects on BP reached an earlier plateau in the NAPA-nonpaced than in the NAPA-paced dogs.

NAPA caused significant reductions in TPR in both NAPA-treated groups. However, the reduction in TPR was of greater magnitude and more closely followed the changes of NAPA plasma concentration in the NAPA-paced dogs than in the NAPA-nonpaced groups. In fact, the response of TPR in this latter group varied during the NAPA infusion. The reduction in TPR peaked early (2–4 min), returned toward baseline (4–10 min), and subsequently decreased again (10–15 min). This multiphasic response occurred even though NAPA plasma concentrations were consistently increasing. Thus, it would appear that the changes in TPR in the NAPA-nonpaced group were not a monotonic manifestation of drug effect. Most likely, the observed TPR pattern represents a complex response to drug induced vasodilatation and hypotension, followed by reflex compensatory vasoconstriction, returning TPR toward baseline (22).

The explanation for the different TPR response between treated groups may lie in NAPA's effect on CO. NAPA reduced CO in the NAPA-nonpaced group by its negative chronotropic effect, since stroke volume did not change or increased above baseline. Thus, the hypotension in NAPA-nonpaced dogs resulted from a decrease in TPR (vasodilation) and a reduced CO. On the other hand, CO was better maintained in NAPA-paced dogs, and in fact, increased initially when SV was augmented. Thus, it appears that changes in flow (CO) affected the TPR response by eliciting reflex compensatory vasoconstriction in NAPA-

nonpaced dogs, perhaps through interaction with low-pressure baroreceptors (22, 23).

When the changes in TPR after NAPA infusion were analyzed in terms of initial TPR, a good correlation was found in the NAPA-nonpaced dogs: the greater the initial TPR, the greater the change induced by NAPA. This is in agreement with previous observation for other vasoactive agents (24, 25). That no such correlation was found in the NAPA-paced dogs may be due to the fact that baseline TPR was lower in these dogs that in nonpaced dogs (Table I).

No consistent change in LVEDP could be demonstrated when either the NAPA-nonpaced or NAPA-paced groups were compared to control dogs. This could simply reflect the great variability encountered in this parameter and does not exclude the possibility that NAPA has venodilator properties.

In summary, in the chloralose/urethane-anesthetized, open chest dog, NAPA exhibits negative chronotropic and vasodilator effects in association with an apparent positive inotropic effect. This seems to be rather unique for a vasodilator, since tachycardia would be expected to result from the reflex response to vasodilatation and hypotension (22, 26, 27). Although the parent drug, PA, shares these negative chronotropic and hypotensive effects, it differs from its active metabolite in that PA has a negative inotropic effect (9, 17). Furthermore, the vasodilation induced by PA seems to be mediated predominantly by ganglionic blockade (28). Although this mechanism is not excluded for NAPA-induced vasodilation, it is of interest that the peripheral resistance increase seen in the nonpaced dogs occurred when the NAPA concentration was increasing and appears to have been reflex mediated. Thus, further studies are needed to determine the mechanism by which NAPA acts as a vasodilator.

The relevance of these hemodynamic changes to the clinical use of NAPA remain to be established. The 25 to 160 μg/ml range of plasma concentrations that we studied in dogs is higher than that usually encountered in man. However, if used intravenously as an acute antiarrhythmic agent, concentrations such as this will most likely be encountered.

Summary. The hemodynamic actions of *N*-acetylprocainamide (NAPA) were investigated in anesthetized, open chest dogs. NAPA pharmacokinetics and effects were correlated for 2 hr after a 15-min NAPA infusion (60 mg/kg) to five nonpaced dogs and four cardiac-paced dogs. Four control dogs received NAPA diluent for comparison. NAPA infusion in *nonpaced* dogs decreased mean arterial pressure (MAP) by 26.5 ± 7.1% (mean ± SE) and total peripheral resistance (TPR) by 15.0 ± 3.7%, but increased myocardial contractile force (MCF) by 33.5 ± 7.5% and reduced heart rate 18.5 ± 3.2%. Significant differences from controls persisted 18, 28, 32, and 60 min for MCF, MAP, TPR, and heart rate, respectively. The changes in TPR were multiphasic and appeared to result from a combination of drug-induced vasodilation and compensatory reflex vasoconstriction. In NAPA-*paced* dogs, MCF was increased similarly by 31.6 ± 5.3%. MAP and TPR decreased by 33.5 ± 5.3 and 29.1 ± 11.8%, respectively. The magnitude and duration of the latter effects (75 and 50 min, respectively) were greater and cardiac output better maintained than in NAPA-nonpaced dogs. This effect on cardiac output probably accounts for a lack of compensatory vasoconstriction in NAPA-paced dogs. NAPA infusion did not consistently change left ventricular end diastolic pressure. However, consistent NAPA plasma concentration–response relationships were observed for MCF, MAP, TPR, and heart rate: thus, we conclude that NAPA is a vasodilator that has negative chronotropic and positive inotropic effects. The mechanisms of these actions require elucidation.

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