Hemodynamic Effects of N-acetylprocainamide Compared with Procainamide in Conscious Dogs

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SUMMARY We examined the hemodynamic actions of clinically relevant i.v. doses (20 mg/kg and 10 mg/kg) of N-acetyl procainamide (NAPA) in conscious dogs preinstrumented with a left ventricular (LV) micromanometer, LV and aortic catheters, and ultrasonic crystals for measurement of LV internal diameter shortening (%ΔD). Within 30 seconds after the 20-mg/kg dose, there were significant increases in heart rate (27 ± 7 beats/min, mean ± SEM; n = 6), maximum dP/dt (655 ± 206 mm Hg/sec), and %ΔD (2.2 ± 0.9%; all p < 0.05). However, by 6 hours after the dose there were reductions compared with control in peak LV pressure (19 ± 9 mm Hg), dP/dt (610 ± 210 mm Hg/sec), and %ΔD (2.3 ± 0.6%; all p < 0.05). In contrast, equimolar doses of procainamide or drug vehicle alone evoked no response, as did NAPA after pretreatment with reserpine (0.25 mg/kg/day for 2 days) or hexamethonium (10–15 mg/kg). These data suggest NAPA produces a biphasic hemodynamic response with enhancement of LV performance early and a decrease later; this response is different from that of the parent compound, procainamide. These effects are likely mediated by the adrenergic nervous system at either a ganglionic or a central level.

N-ACETYL PROCAINAMIDE (NAPA), a major metabolite of procainamide in man, possesses antiarrhythmic properties independent of its parent compound. Additionally, NAPA has a longer plasma half-life and a lower incidence of the drug-induced systemic lupus syndrome than procainamide, which may afford distinct clinical advantages. Although the pharmacologic properties of NAPA have not been well characterized, recent studies in anesthetized dogs indicate that the electrophysiologic effects of NAPA and procainamide are dissimilar, suggesting that the antiarrhythmic mechanisms may be different. Also, preliminary data indicate that the hemodynamic properties of the two agents differ. Intravenous procainamide has been variably shown to cause hypotension and depression of left ventricular (LV) performance, whereas NAPA may enhance LV function and not affect blood pressure.

In the present investigation, we sought to clarify the hemodynamic effects of NAPA compared with procainamide in an animal model. We studied conscious, preinstrumented dogs, using i.v. doses that would have clinical relevance in humans. The extent to which such effects were modulated by the adrenergic nervous system was also assessed by pharmacologic pretreatment with reserpine or hexamethonium, compounds that block adrenergically mediated responses at different levels in the sympathetic nervous system.

Methods

Twelve adult mongrel dogs (15–25 kg) were studied after recovery from surgery, during which devices for measuring LV performance were implanted. Serial hemodynamic measurements were performed in the conscious state after administration of NAPA, procainamide and drug vehicle alone as an i.v. bolus. In a subgroup of five dogs, NAPA was again administered after pretreatment with reserpine or hexamethonium to block and localize effects mediated by the adrenergic nervous system.

Specifically, the dogs were anesthetized with sodium pentobarbital, 25 mg/kg i.v., and ventilated with a Harvard respirator. Using a sterile technique, the heart was exposed through a thoracotomy in the left fifth intercostal space. A solid-state pressure transducer (P18, Kongsberg Instruments, Inc.) and a polyvinyl catheter for transducer calibration (inner diameter 1.1 mm) were inserted into the LV cavity through an apical stab wound. Two ultrasonic crystals were implanted in the left ventricle on the endocardial surface of the anterior and posterior walls to measure the diameter of a transverse chord. Each crystal consisted of a 5-MHZ piezoelectric disc, 4 mm in diameter, with two 29-gauge copper wires soldered to either side and coated with a 1-mm-thick spherical resin lens. Polyvinyl catheters were also implanted in the descending aorta and left atrium of all dogs. The chest was closed, the wires and tubes were tunneled subcutaneously to the back of the neck, and the dogs were allowed to recover for at least 2 weeks.

The dogs were trained to lie quietly on their right side during studies. The aortic and LV catheters were connected to Statham P23Db pressure transducers calibrated from a mercury manometer; the zero reference point was at the level of the vertebral column. The LV pressure signal from the micromanometer was adjusted to match that obtained from the fluid-filled catheter. The first derivative of LV pressure was obtained by differentiating the micromanometer signal electronically using an RC circuit, a system with a linear frequency response to 70 Hz and 3 db down at 100 Hz. The transit time of 5 MHz sound between each crystal pair was determined using the electronics of Franklin and Kemper and converted to distance, assuming a constant velocity of sound in blood of 1.55 m/msec. LV pressure, the first deriva-
tive of LV pressure (dP/dt), the minor diameter signal and aortic pressure were recorded on a Beckman RM oscillograph at a paper speed of 25 mm/min. To determine actual values of individual measurements, data were collected at 25 mm/sec, averaging 15 consecutive cardiac cycles.

Protocol

Serial Hemodynamic Effects of NAPA or Drug Vehicle

During experiments, the dogs were unsedated and resting in a sling. After obtaining control data over a 10-minute period, 20 mg/kg of NAPA, supplied as a 1% solution of NAPA-HCl in sterile water (supplied by Arnar-Stone Pharmaceuticals), were injected over a 1-minute period. Data were taken at 30 seconds, 3 minutes, 30 minutes, 1 hour, 3 hours, and 6 hours after injection. After the first hour and third hour of data collection, the dogs were returned to their cages and reconnected to the recording devices 15 minutes before the next data point; this was done to eliminate hemodynamic changes due to agitation from prolonged monitoring. On separate days, at least 48 hours after administration of the initial drug, 10 mg/kg of NAPA or drug vehicle were infused exactly as in the first study.

Serial Hemodynamic Effects of Procainamide

In a separate group of five dogs, an equimolar dose of procainamide (Pronestyl, E. R. Squibb & Sons), 18.3 mg/kg, supplied as a commercially available 10% solution, was administered intravenously according to the same protocol.

Effects of Adrenergic and Ganglionic Blockade on the Hemodynamic Response to NAPA

To assess the role of the adrenergic nervous system in mediating the hemodynamic response to NAPA, five dogs were pretreated with intramuscular reserpine, 0.25 mg/kg/day for 2 days, or i.v. hexamethonium, 10–15 mg/kg, on separate occasions at least 3 weeks apart. This regimen of reserpine has been previously shown to deplete norepinephrine from adrenergic nerve terminals, and effectiveness of such blockade was further assessed by a flat arterial pressure response to i.v. tyramine, 0.1 mg/kg. Completeness of the nicotinic blockade at sympathetic ganglia was judged by the failure of additional hexamethonium to further alter heart rate, arterial pressure or dP/dt. After reserpine pretreatment, NAPA, 20 mg/kg, was given as before and data were collected for 6 hours after treatment. After hexamethonium pretreatment, NAPA, 20 mg/kg, was administered and data were collected for only 1 hour.

FIGURE 1. Analog recording from a typical dog after i.v. administration of 20 mg/kg of n-acetylprocainamide (NAPA). By 3 minutes after NAPA, heart rate, peak dP/dt and percent minor diameter shortening increased. By 6 hours, however, arterial pressure, dP/dt and percent shortening decreased. LV = left ventricular; % minor diameter shortening = (end-diastolic diameter – end-systolic diameter) × 100/end-diastolic diameter.
TABLE 1. Hemodynamic Variables After Drug Administration

<table>
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<tr>
<th></th>
<th>Control</th>
<th>30 sec</th>
<th>3 min</th>
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<tr>
<td>NAPA (20 mg/kg; n = 6)</td>
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<tr>
<td>HR (beats/min)</td>
<td>74 ± 7</td>
<td>101 ± 13*</td>
<td>95 ± 13*</td>
</tr>
<tr>
<td>AoP* (mm Hg)</td>
<td>123 ± 5/79 ± 4</td>
<td>127 ± 4/85 ± 3</td>
<td>123 ± 4/82 ± 3</td>
</tr>
<tr>
<td>Mean</td>
<td>97 ± 5</td>
<td>102 ± 5</td>
<td>102 ± 5</td>
</tr>
<tr>
<td>EDP (mm Hg)</td>
<td>9 ± 1</td>
<td>7 ± 2*</td>
<td>8 ± 2</td>
</tr>
<tr>
<td>EDD (mm)</td>
<td>39.0 ± 3.4</td>
<td>38.4 ± 3.3</td>
<td>38.6 ± 3.5</td>
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<tr>
<td>%ΔD</td>
<td>22.0 ± 4.1</td>
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<tr>
<td>dP/dt (mm Hg/sec)</td>
<td>3123 ± 234</td>
<td>3778 ± 206*</td>
<td>3343 ± 224</td>
</tr>
</tbody>
</table>

| NAPA (10 mg/kg; n = 6) |                  |              |              |
| HR (beats/min)         | 79 ± 5           | 88 ± 5       | 85 ± 5       |
| AoP (mm Hg)            | 108 ± 2/69 ± 3   | 112 ± 2/75 ± 3 | 110 ± 1/72 ± 2 |
| Mean                   | 87 ± 1           | 92 ± 2       | 92 ± 2       |
| EDP (mm Hg)            | 7 ± 1            | 8 ± 2        | 8 ± 2        |
| EDD (mm)               | 41.2 ± 4.4       | 41.0 ± 4.4   | 41.0 ± 4.3   |
| %ΔD                    | 19.4 ± 4.3       | 20.9 ± 4.6   | 20.5 ± 4.5   |
| dP/dt (mm Hg/sec)      | 2785 ± 178       | 3170 ± 207*  | 2870 ± 130   |

Procainamide (18.3 mg/kg; n = 5) |                  |              |              |
| HR (beats/min)          | 89 ± 7           | 95 ± 11      | 90 ± 10      |
| AoP (mm Hg)             | 115 ± 4/72 ± 3   | 117 ± 6/77 ± 3 | 116 ± 3/77 ± 2 |
| Mean                    | 88 ± 3           | 94 ± 5       | 92 ± 2       |
| EDP (mm Hg)             | 7 ± 2            | 7 ± 2        | 6 ± 2        |
| EDD (mm)                | 36.8 ± 2.7       | 36.6 ± 2.7   | 36.9 ± 2.8   |
| %ΔD                    | 20.5 ± 2.1       | 20.4 ± 1.9   | 20.5 ± 1.9   |
| dP/dt (mm Hg/sec)       | 2932 ± 269       | 2949 ± 230   | 2900 ± 241   |

Drug vehicle (n = 6) |                  |              |              |
| HR (beats/min)         | 64 ± 4           | 65 ± 6       | 65 ± 5       |
| AoP (mm Hg)            | 119 ± 8/79 ± 7   | 118 ± 9/77 ± 5 | 119 ± 10/78 ± 6 |
| Mean                   | 92 ± 8           | 90 ± 6       | 91 ± 7       |
| EDP (mm Hg)            | 9 ± 1            | 9 ± 1        | 9 ± 1        |
| EDD (mm)               | 43.4 ± 5.2       | 43.5 ± 5.2   | 43.7 ± 5.2   |
| %ΔD                    | 29.2 ± 3.8       | 29.2 ± 3.8   | 29.3 ± 3.8   |
| dP/dt (mm Hg/sec)      | 2992 ± 419       | 2992 ± 419   | 3036 ± 446   |

Values are mean ± SEM.
*Different from control (p < 0.05).
†Systolic/diastolic.

Abbreviations: NAPA = n-acetylprocainamide; HR = heart rate; AoP = aortic pressure; EDP = end-diastolic pressure; EDD = end-diastolic diameter; %ΔD = percent minor diameter shortening; dP/dt = maximum first derivative of left ventricular pressure.

Procainamide and NAPA Serum Concentration Determinations (n = 4)

Five milliliters of blood were drawn at 30 seconds, 3 minutes, 10 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours and 5 hours after 20 mg/kg of NAPA in four dogs to determine serum NAPA concentrations. The serum was immediately separated by centrifugation and frozen at −4°C until analysis. Serum concentrations of NAPA and procainamide in each sample were determined by a specific high-performance liquid chromatography assay.8 Drugs were extracted from serum into ethyl acetate after alkalization with 1 ml of 1 N sodium hydroxide. The lower limit of sensitivity of the assay was 0.5 μg/ml for NAPA and procainamide.

Data Analysis

Statistical evaluation was performed by analysis of variance with repeated measures of the same parameter. Individual means after the drug were compared with control means using the Dunnett’s t test.11 The level of significance was chosen as p ≤ 0.05.

Results

Effects of NAPA with Intact Sympathetic Control (table 1)

Figure 1 shows representative oscillograph recordings of a typical dog given 420 mg of i.v. NAPA. Within 30 seconds after drug administration, there were small increases in heart rate, maximum dP/dt
(dP/dt max), and extent of minor-axis shortening persisting to 3 minutes. End-diastolic pressure and dimension fell slightly, concomitant with the rise in heart rate, but arterial pressure (systolic, diastolic and mean) was unchanged. These effects had abated by 30 minutes, but continued serial recordings demonstrated a reduction in dP/dt max and extent of shortening by 3 hours compared with control. At 6 hours, these late changes were most marked, showing a 30% reduction in shortening and dP/dt max, as well as a 10-mm drop in peak LV pressure compared with predrug levels.

Similar data were obtained from the other five dogs in response to high-dose NAPA (table 1, fig. 2). Within 30 seconds there were significant increases in heart rate (27 ± 7 beats/min; mean ± SEM), dP/dt (655 ± 206 mm Hg/sec), and percent minor diameter shortening (2.2 ± 0.9%). These increases were still present at 3 minutes, but not by 30 minutes when all values except heart rate had returned to control. However, reductions in arterial pressure, dP/dt max, and percent minor-axis shortening appeared by 3 hours after the drug. These reductions were maximal by 6 hours, when peak LV pressure was decreased by 19 ± 9 mm Hg (15%), dP/dt by 610 ± 210 mm Hg/sec (20%), and percent minor diameter shortening by 2.3 ± 0.6% (10%) from control (all p ≤ 0.05). Figure 2 shows hemodynamic measurements with significant serial changes in response to high-dose NAPA. None of these measurements was significantly altered after infusion of an identical volume of the drug vehicle alone (table 1).

Intravenous administration of 10 mg/kg of NAPA under identical experimental conditions showed similar but less marked alterations compared with the 20-mg/kg dose (fig. 2, table 1). There were slight (<10%) but nonsignificant early increases in heart rate, dP/dt max, and percent shortening. At 6 hours, there were nonsignificant reductions in dP/dt max, peak LV pressure, and percent minor diameter shortening compared with control. Thus, the effects of NAPA appeared to be dose-related.

### Table 1. (Continued)

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Drug Levels

Serum concentrations of NAPA at 0.5, 1, 2, 3, 4 and 5 hours after drug administration are shown in figure 3. There was initially a rapid distribution phase, followed by a slower elimination phase with a half-life for NAPA of approximately 4 hours. No detectable levels of procainamide were present in any of the NAPA serum samples. Similarly, in four dogs in which procainamide was given, no NAPA was present. Thus, the early hemodynamic effects of NAPA administration correlated with peak serum levels of the drug. However, because the late effects were associated with negligible serum levels, the decrease in systolic pressure, percent minor diameter shortening, and dP/dt max 6 hours after NAPA were not directly related to the quantity of drug in the serum.

Effects of Procainamide

To assess the potentially different hemodynamic properties of procainamide and NAPA, equimolar doses of procainamide (18.3 mg/kg, equivalent to 20 mg/kg NAPA) were given under the same experimental conditions (fig. 4). No early responses to procainamide were noted, compared to the increases in heart rate, dP/dt max, and percent shortening noted at 30 seconds with NAPA. By 6 hours, although there were downward trends in peak LV pressure and dP/dt max after procainamide, the values were not statistically different from control. Thus, i.v. procainamide at 18.3 mg/kg had no hemodynamic effects in conscious dogs followed for 6 hours.

Figure 2. Hemodynamic effects of 20 mg/kg and 10 mg/kg of n-acetylpredonainamide (NAPA) in six dogs over 6 hours. Measurements represent group means ± SEM at times indicated. After the 20-mg/kg dose, heart rate, left ventricular (LV) dP/dt and percent minor diameter shortening increased significantly, whereas significant decreases in LV pressure, dP/dt, and percent shortening were evident by 6 hours. Effects at the 10-mg/kg dose were similar but not as pronounced as at the high dose. Asterisks denote statistically significant differences from control (p ≤ 0.05).

Figure 3. Serial serum n-acetylpredonainamide (NAPA) concentrations obtained from four dogs after 20 mg/kg of NAPA. Measurements represent group means ± SEM at times indicated. Peak levels of NAPA corresponded to early positive inotropic action of the drug. However, the late hemodynamic decline at 4–6 hours was associated with the lowest serum levels.
HEMODYNAMIC EFFECTS OF NAPA/Badke et al.

in heart rate, maximum dP/dt, and percent minor
diameter shortening early, followed by a decrease in
arterial pressure, maximum dP/dt, and percent minor
diameter shortening late. Thus, both an isovolumic
and ejection phase index of LV performance improve
immediately after NAPA infusion despite decreasing
preload (i.e., end-diastolic dimension or pressure),
suggesting that the drug initially augments myocardial
contractility. Of course, such a positive inotropic
action might be mediated by the heart rate increase
(i.e., the Bowditch phenomenon), but the tachycardia
alone (average increase of 26 beats/min) would not be
expected to account for the increase in dP/dt max
(average 21% increase), based on the data of Barnes et
al., who found only a 12% increase in dP/dt max with
an increase of 30 beats/min in heart rate.12

The decline in dP/dt max and percent minor

Effects of Autonomic Blocking Agents

The results of high-dose NAPA administration (20
mg/kg) after pretreatment with reserpine are shown in
figure 5 and table 2. The early increases in heart rate,
dP/dt max, and percent minor diameter shortening at
30 seconds after NAPA in dogs with intact sympa-
thetic control were absent in reserpinized dogs.
Similarly, the declines in systolic pressure, dP/dt max,
and percent minor diameter shortening at 6 hours
were also prevented by pretreatment with reserpine.
Thus, NAPA had no detectable hemodynamic effects
in dogs with absent adrenergic mechanisms.

To identify the site of action of NAPA in the sympa-
thetic nervous system, hexamethonium was also ad-
ministered before high-dose NAPA infusion in five
dogs. Hexamethonium resulted in an 80% (64 ± 6
beats/min) increase in heart rate, a 6% (4 ± 6 mm Hg)
decrease in mean arterial pressure, and a 19% (577 ±
141 mm Hg/sec) reduction in dP/dt max (table 2).
After nicotinic blockade, infusion of 20 mg/kg of
NAPA failed to elicit additional significant hemo-
dynamic changes within 1 hour.

Discussion

Our results suggest that the hemodynamic response
to NAPA administration is biphasic, with an increase

FIGURE 4. Hemodynamic effects of 20 mg/kg of n-acetyl-
procainamide (NAPA) compared with equimolar (18.3
mg/kg) procainamide (n = 5; p < 0.05). Measurements
represent group means ± SEM at times indicated. In general,
procainamide had no serial hemodynamic effects in con-
scious dogs over 6 hours.

FIGURE 5. Hemodynamic effects of 20 mg/kg n-acetyl-
procainamide (NAPA) in five dogs before and after pre-
treatment with reserpine, 0.25 mg/kg per day for 2 days.
Measurements represent group means ± SEM at times
indicated. Asterisks denote statistically significant differ-
ences from control (p < 0.05). Early and late hemodynamic
actions of NAPA were blocked by inhibition of adrenergic
neurotransmission. LV = left ventricular.
diameter shortening at 6 hours after infusion suggests that NAPA has negative inotropic properties late. Moreover, the reductions in these measurements are present in the face of a decrease in peak systolic LV pressure (or mean arterial pressure), indicating a decrease in LV afterload. The latter alone, in the presence of an unchanged preload, would be expected to augment percent shortening and have little effect on dP/dt max in conscious animals.13

The biphasic response of NAPA, with tachycardia and contractile enhancement early and hypotension and inotropic depression late, is similar to that of drugs that act on the adrenergic nervous system (e.g., guanethidine or bretylium). For example, bretylium elicits a similar hemodynamic response by initially releasing norepinephrine from nerve terminals and then by blocking reuptake.14 Thus, we investigated whether the effects of NAPA might be sympathetically mediated by administering it after pretreatment with reserpine, which depletes neurotransmitter (norepinephrine) from adrenergic nerve terminals. The observation that pretreatment blocks both the early and late hemodynamic response to NAPA suggests that the drug does act through the sympathetic nervous system. The early response is also blocked by hexamethonium, a nondepolarizing ganglionic blocking agent, indicating that NAPA's site of action may be at the ganglion (i.e., a depolarizing blocker) or central nervous system, but not at the level of the adrenergic nerve terminal. We conclude that the hemodynamic effects of NAPA are probably indirect, mediated initially through enhancement and then depression of sympathetic nervous activity.

This mechanism of action may help to explain why the late hemodynamic properties of NAPA are unrelated to serum levels. In particular, the drug may act by releasing and then by blocking the reuptake of neurotransmitter. During the phase of blockade, the neurotransmitter would be metabolized, requiring re-synthesis before normal adrenergic nerve activity could be restored. Alternatively, the drug might concentrate in nervous tissue. In any event, a disparity between serum concentration and maximal physiologic action is not uncommon for agents whose effects are sympathetically mediated (e.g., α methyldopa or reserpine).15,16 Moreover, a dissociation between drug levels and electrophysiologic properties has also been noted for NAPA by Jaillon and Winkle,4 who reported that NAPA's prolongation of the QT interval, ventricular refractory period, and Wenckebach cycle length were maximal during the postinfusion period, when plasma levels were decreasing.4 Although these findings might be related to differences between plasma and cardiac tissue concentration, an alternative explanation is that the electrophysiologic properties are also in part mediated by adrenergic mechanisms; this needs further investigation.

The hemodynamic effects of NAPA and its parent compound, procainamide, when given in equimolar concentrations, are different. Procainamide has been variably reported to depress or not to change myocardial contractility and to decrease or not to change arterial pressure, largely as a function of the experimental model.4,17-19 Thus, in anesthetized dogs, procainamide clearly possesses vasodilatory properties that are secondary to inhibition of sympathetic ganglionic transmission, as demonstrated by Schmid et al.20 In conscious dogs, however, similar doses of procainamide have not depressed LV function or reduced arterial pressure.18,19 Our data are in agreement with these latter studies, in that no hemodynamic response to 18.3 mg/kg of procainamide was elicited. However, we have shown that NAPA does have hemodynamic actions that appear to be mediated through the sympathetic nervous system, similar to the findings of Schmid et al. for procainamide. Perhaps the two drugs have different sites of action or a different potency at similar sites, which may be considerably modified by general anesthesia.

The biphasic hemodynamic actions of NAPA reported here have not been previously described, although preliminary studies have reported data similar to ours early after drug administration. Thus, in anesthetized, atrially paced dogs with myocardial infarction, NAPA had positive inotropic activity when given as a prolonged infusion.8 Also, preliminary data in man suggest an enhanced contractile response.21

The effects of NAPA on heart rate, which have been
more extensively investigated, are more controversial. Our study suggests that sinus tachycardia occurs early but is transient. This finding is consistent with the data of Strong et al., who administered 500 mg of i.v. NAPA to three normal human subjects and noted sinus tachycardia in two early after initiating the infusion (within 6 minutes).25 Jaillon and Winkle, Bagwell et al., and Amlie et al.26 noted a decrease in heart rate after i.v. NAPA administration in dogs. Failure to observe an early tachycardia in these studies may have been secondary to general anesthesia with high levels of resting sympathetic tone (initial heart rate > 110 beats/min in all three) or failure to obtain measurements immediately after drug administration. Also, the degree of tachycardia appears to be dose-dependent for NAPA, and perhaps the high serum levels achieved early and rapidly in our study by bolus injection were not produced in these others. In any event, it would be tempting to attribute this early tachycardia to possible vagolytic action of NAPA, a property that has been ascribed to the parent compound, procainamide.19 However, the early heart rate response to NAPA was obliterated by pretreatment with reserpine, which blocks sympathetic but not parasympathetic stimulation to the sinus node. We conclude that the early tachycardia after NAPA administration is probably a result of sympathomimetic rather than vagolytic effects.

The decrease in arterial pressure, dp/dt max, and percent minor diameter shortening 6 hours after 20 mg/kg of NAPA has not been observed previously. In most studies, hemodynamic recording was discontinued before the onset of these late actions. However, the study of Jaillon and Winkle4 was continued for a total of 6 hours after initial NAPA administration, and although average mean arterial pressure was reduced 5 mm Hg from control at 6 hours, this was not a statistically significant decrease. Perhaps this was a result of the lower plasma levels achieved early in their study (i.e., < 15 µg/ml during the initial 60 minutes) or to the effects of chloralose anesthesia. In this regard, chloralose may depress inotropic state and systemic vascular resistance may rise significantly during prolonged chloralose administration.24 This latter circumstance may have prevented NAPA-induced hypotension in their study, which appears to be secondary to adrenergic inhibition from our data.

The clinical relevance of these hemodynamic effects must be defined. The early tachycardia and improvement in ventricular performance appears to be both transient and dose-related, with minimal effects at the 10-mg/kg bolus dose. At stable levels that may be effective in suppressing ventricular premature complexes in man (approximately 11 µg/ml),28 we saw no hemodynamic changes. Therefore, in patients requiring i.v. NAPA in whom tachycardia might be deleterious, several boluses might be preferable to one large loading dose before beginning a continuous infusion. The late depressant effects are potentially of greater concern. We gave NAPA as a single bolus dose to achieve high initial levels and then observed the hemodynamic effects 6 hours later. Whether these findings would be apparent 6 hours after a continuous infusion to maintain a constant lower plasma level of drug is unknown. Similarly, the NAPA released by procainamide metabolism after injection of the parent compound might not elicit the same responses that we observed. Certainly, the possibility that NAPA might cause late hemodynamic depression should be considered. Although the degree of alteration in hemodynamic variables in normal subjects appears small, in patients with depressed ventricular function, NAPA might worsen congestive heart failure or produce systemic hypotension.

We have demonstrated that NAPA may have hemodynamic properties that are different from those of its parent compound, procainamide. The circulatory response to NAPA is biphasic, with an early increase in heart rate and contractile performance, and a late reduction in arterial pressure and inotropic state. These effects appear to be mediated by adrenergic mechanisms, and NAPA may stimulate and then block sympathetic nervous transmission at either the ganglionic or central level. Future studies may clarify whether such actions mediated by the sympathetic nervous system may also play some role in the antiarrhythmic properties of the drug.

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Digitalis-associated Cardiac Mortality After Myocardial Infarction

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SUMMARY The effect of digitalis therapy on 4-month posthospital cardiac mortality was investigated in 812 patients who survived the hospital phase of acute myocardial infarction. A stepwise multiple logistic regression analysis was used to identify variables associated with increased mortality and to adjust for differences in confounding variables between digitalis and nondigitalis patients. The major 4-month mortality (10 of 26 patients [38.5%]) occurred in digitalis-treated patients with congestive heart failure in the coronary care unit and complex ventricular premature depolarizations (VPDs) on a predischARGE Holter recording. Logistic analyses that controlled for confounding variables indicated that digitalis use contributed to the increased mortality rate in this high-risk subset. The predicted mortality difference due to digitalis in patients with congestive heart failure and complex VPDs, adjusted for relevant nondigitalis risk factor variables, was 30% (90% confidence interval 18–42%). This retrospective study suggests that digitalis use increases the early posthospital mortality of myocardial infarction patients with combined electrical and mechanical dysfunction.

DIGITALIS THERAPY has been a mainstay in the treatment of left ventricular failure in patients with and without coronary heart disease. Some caution has developed regarding the use of cardiac glycosides in patients with acute myocardial infarction because of the hazards of arrhythmic toxicity and the potentially harmful effect of enhanced myocardial oxygen consumption.¹ ² Katz³ suggested that the diseased heart operates under optimal conditions, and further inotropic stimulation (as with digitalis) could have adverse effects. Katz warned that drugs that increase contractility in the diseased heart may produce a benefit at the expense of life-shortening myocardial damage.

Digitalis is most useful in controlling the ventricular response rate to atrial fibrillation. The clinical efficacy of long-term digitalis therapy in patients with chronic left ventricular dysfunction and sinus rhythm has been questioned.⁴ ⁵ Some physicians believe from their own clinical experience that digitalis therapy may increase the short-term mortality of convalescent myocardial infarction patients beyond that expected on the basis of the patients' anticipated clinical course.

We analyzed the data base of the Rochester Heart Research Follow-Up Program⁶ to determine whether postinfarction patients treated with cardiac

Hemodynamic effects of n-acetylprocainamide compared with procainamide in conscious dogs.

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