Electrophysiologic Comparative Study of Procainamide and N-Acetylprocainamide in Anesthetized Dogs: Concentration-Response Relationships

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SUMMARY The electrophysiologic effects of n-acetylprocainamide (NAPA) and procainamide (PA) were compared in 14 chloralose-anesthetized dogs using intracardiac electrography and programmed stimulation. With five successive sequences of an intravenous bolus followed by a 45-minute infusion, plasma concentrations (Cp) ranged from 1.8 ± 0.1 to 32 ± 2 μg/ml for PA and from 8.2 ± 0.3 to 125 ± 7 μg/ml for NAPA. In three control dogs, mean aortic pressure (BP), heart rate (SCL), sinus node recovery time (SNRT), conduction times (ah, HV and QRS), ventricular repolarization time (QTc), Wenckebach cycle length (WCL) and atrial, nodal and ventricular refractory periods (RP) had a mean coefficient of variation < 9%. Neither drug significantly changed BP and sinus node automaticity (SCL or SNRT). PA was considerably more effective than NAPA in producing a Cp-dependent increase of conduction times. NAPA exerted limited effect only on HV (max increase 13 ± 3.3% [SEM] at Cp = 125 ± 7 μg/ml). NAPA and PA were equally effective in producing parallel Cp-dependent increases of QTc and WCL. Atrial RPs were prolonged by both drugs with parallel Cp response curves and PA was slightly more potent than NAPA. The PA Cp-dependent increase of nodal functional RP was greater than the effects of NAPA and the Cp-response curves were not parallel. Both drugs increased ventricular RP. The maximum effect of PA always occurred at the highest drug concentration, while the peak effect of NAPA on some measured parameters occurred during the postinfusion decay period. We conclude that in addition to differences in pharmacokinetics NAPA and PA may have different mechanisms of action, different effective antiarrhythmic concentrations and different electrical cardiac toxicities.

PROCAINAMIDE pharmacokinetic studies in man show that n-acetylprocainamide (NAPA) is the major metabolite of procainamide.1-8 Studies in animal arrhythmia models5,9-11 and in man12 indicate that NAPA exerts antiarrhythmic effects that may be partly responsible for the antiarrhythmic effect of procainamide.6 Initial studies suggest that NAPA may not have the same propensity to induce systemic lupus as procainamide.9 If these observations are correct, NAPA might become an alternative antiarrhythmic drug.

To investigate the mechanism of the antiarrhythmic action of NAPA, several electrophysiologic studies in isolated tissue preparations11,12 have shown that some effects of NAPA and procainamide were different. In the dog heart in situ, Amlie et al.14 found that NAPA did not increase His-Purkinje and atrioventricular (AV) nodal conduction times and was less potent than procainamide in increasing the AV nodal functional refractory period. However, they used only two drug doses and did not find a significant correlation between the electrophysiologic effects and plasma drug concentration (Cp).

In the present study we compared the electrophysiologic properties of NAPA and procainamide in closed-cage, anesthetized dogs using His bundle electrography and programmed electrical stimulation. The effects of the drugs were examined over a wide range of Cps achieved by different intravenous infusion rates.

Methods

General Procedures

Seventeen mongrel dogs of either sex (19-31 kg, average 24 kg) were anesthetized with morphine sulfate 2 mg/kg subcutaneously, followed 30 minutes later by α-chloralose 200 mg/kg intravenously (4% solution in polyethylene glycol and distilled water). The dogs were intubated with a cuffed endotracheal tube. Artificial ventilation was maintained with a Harvard respirator pump using humidified room air. A large polyethylene catheter was inserted into the left femoral artery to monitor the systemic arterial pressure using a Statham P23Db transducer. The mean arterial blood pressure was calculated using the formula BP = diastolic pressure + 1/3 of the pulse pressure.15 The same catheter was used to draw blood samples for arterial blood gas analysis using a Corning model 165 blood gas analyzer. Depth and rate of respiration were adjusted to maintain an arterial Po2 over 72 mm Hg and pH between 7.35 and 7.44 throughout the experiment. A catheter was placed in the left femoral vein for administration of additional anesthetic, which was given hourly (10 ml of 4% chloralose solution) to

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maintain deep anesthesia. The left jugular vein was catheterized for drug infusion. Surface leads II and III of the ECG were continuously monitored.

Electrophysiologic Studies

Sinus cycle length (SCL), intraventricular conduction times (QRS) and QT interval (corrected QTc according to the Bazett formula) were measured at the spontaneous sinus rate using the external ECG and a recording speed of 100 mm/sec.

A USCI #7F tripolar electrode catheter was positioned via the right carotid artery in the root of the aorta at the level of the aortic cusps to record His bundle electrograms. This signal was preamplified and filtered (20 and 200 Hz) and displayed on a Tektronix oscilloscope at a speed of 1000 mm/sec. A picture of the HV interval was then taken using a Polaroid C-5 oscilloscope camera. His bundle-to-ventricular activation time (HV) was measured from the beginning of the bundle of His electrogram to the earliest ventricular depolarization recorded on the intracardiac electrogram. This arrangement allows measurement of HV interval to within ±1.0 msec. Care was taken throughout the experiment to be certain that the onset of this intracardiac ventricular electrogram maintained a constant relationship to the earliest ventricular activation in any surface or intracardiac lead. AH was the interval from the beginning of the atrial depolarization (A) to the beginning of the bundle of His bipolar electrogram (H) measured at 100 mm/sec.

Two additional USCI electrode catheters were positioned, one tripolar into the right ventricle via the right femoral vein and one quadrupolar in the right atrium via the right jugular vein. The two distal electrodes of the right atrial and the right ventricular catheters were connected to a model 850A stimulus isolation unit of a programmable stimulator (W.P. Instruments, preset control 842, interval generator 830, pulse modules 831A). The signal from the two proximal electrodes of the right atrial catheter was preamplified, filtered (20–200 Hz) and recorded in order to permit accurate recognition of the atrial depolarization during the studies of AV nodal refractory periods.

The functional and effective refractory periods of the right ventricle (VFRP and VERP, respectively) were determined when the ventricle was paced at a fixed cycle length (300 msec) using a 2-msec duration rectangular pulse S1 and a twice-diastolic-threshold intensity (mean diastolic ventricular threshold = 0.8 mA ± 0.16 [SEM]). A premature ventricular stimulus S2 of same duration and intensity as S1 was delivered after every eight regularly delivered S1 stimuli at progressively shorter intervals (20-msec steps from 260 to 200 msec, then 10-msec steps) until S2 failed to depolarize the ventricle. Each S2 was followed by a 1200-msec pause of stimulation in order not to interfere with the cardiac spontaneous response to S2. The VFRP was defined as the shortest attainable V1V2 interval, and the VERP as the longest S1S2 interval.

When S2 failed to depolarize the ventricle, A similar procedure was used to determine the effective and functional atrial refractory periods (AERP and AFRP, respectively) and AV nodal refractory periods (NERP and NFRP, respectively), using right atrial pacing at a fixed cycle length (300 msec) with a 2-msec duration rectangular pulse S1 and a twice-diastolic threshold intensity (mean atrial threshold = 0.9 ± 0.1 mA). The premature atrial impulse S2 had the same characteristics as S1, A1, H1, V1 were, respectively, the atrial, bundle of His and ventricular responses to the driven stimulus S1, A2, H2, V2 were, respectively, the atrial, bundle of His and ventricular responses to the premature extrastimulus S2. The measurement of the refractory periods and of the AV and HV intervals were made at the same driven cycle length throughout each experiment. The driven atrial cycle length determining the Wenckebach phenomenon (WCL) was determined using a progressively increasing frequency of atrial stimulation (driven cycle length decreased by 10 msec every 30 seconds) until second-degree type I AV block first appeared.

To study the automaticity of the sinoatrial node, the post-overdrive pacing pause of sinus node recovery time (SNRT) was measured according to Mandel et al.

All the recordings were done on an eight-channel Honeywell 1508 visicorder at a paper speed of 100 mm/sec.

Protocols

The effects of NAPA were studied in eight dogs and the effects of procainamide in six dogs. The doses of NAPA and procainamide (table 1) were chosen using the kinetics data of Baer et al. to reach rapidly five Cps of either NAPA or procainamide in each dog and to maintain each concentration nearly constant during the time (approximately 10–15 minutes) necessary to make a complete set of electrophysiologic measurements. Thus, each animal received five successive sequences of either NAPA or procainamide, and each sequence included an intravenous bolus injection (loading dose) immediately followed by a slower intravenous infusion over 45 minutes. All infusions were

| Table 1. Doses of Procainamide and N-Acetylprocainamide Used for the Five-bolus Injections and 30-minute Infusions |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| N-acetylprocainamide (n = 8) | | | | | |
| Bolus inj. (mg/kg) | 8.5 | 8.5 | 17 | 34 | 68 |
| Infusion (µg/kg/min) | 25 | 50 | 100 | 200 | 400 |
| Procainamide (n = 6) | | | | | |
| Bolus inj. (mg/kg) | 2.8 | 2.8 | 5.6 | 11.2 | 22.4 |
| Infusion (µg/kg/min) | 14 | 28 | 56 | 112 | 224 |
by a constant speed Harvard infusion pump. Blood pressure was recorded and the electrophysiologic measurements were made before the first injection (basal values), and between 30–45 minutes of each of the five intravenous infusions. Blood for drug concentration determination was drawn from the left femoral artery catheter at 15 minutes, 30 minutes and 45 minutes of each of the five infusions. During the drug concentration decay period after the last infusion, blood pressure and electrophysiologic measurements were recorded and blood was drawn for Cp determination at 30 and 60 minutes postinfusion in all dogs, and at 120 minutes in five dogs receiving NAPA and six dogs given procainamide. The protocol is summarized in figure 1.

In a control group of three dogs, saline was injected instead of drugs using the same five successive sequences of intravenous bolus and intravenous infusion. Blood pressure and the electrophysiologic parameters were recorded before the first injection (basal values), between 30 and 45 minutes of each of the five intravenous infusions, and 30 minutes, 60 minutes, and 120 minutes after the end of the last infusion.

Drugs

NAPA was supplied* in a 1% solution of NAPA HCl in sterile distilled water. The procainamide used was a commercially available preparation of procainamide hydrochloride (Pronestyl, Squibb Lab) 10% solution. All the dilutions were made using distilled water. A previous HPLC analysis in our laboratory had shown that there was no NAPA present in the procainamide solution and no procainamide present in the NAPA solution.

Procainamide and NAPA Concentration Determinations

Five milliliters of blood were drawn for each determination. The plasma was immediately separated by centrifugation and frozen until analysis. Cp of both drugs were determined by a specific, high-performance liquid chromatography assay modified with ion-paired chromatography. Drugs were extracted from plasma into ethyl-acetate after buffering with sodium bicarbonate pH 10. The lower limit of sensitivity of the assay was 0.1 μg/ml for NAPA and procainamide.

Data Analysis

All data are presented as mean ± SEM. For each dog, the blood pressure and electrophysiologic data measured during and after the five infusions of NAPA or procainamide were expressed as percentage of change compared to the basal values. The two-tailed t test was used to compare the basal values in the two groups of dogs (unpaired data). Log-linear regression analyses were performed in each dog to determine the relationship between the logarithm of the plasma concentration of NAPA or procainamide and individual electrophysiologic effects expressed in terms of percent change. Mean slopes of the regression lines were obtained in each group and the one-tailed t test was used to test the difference of mean slopes from 0 and the independent group t test to compare mean slopes between the two groups. The level of significance was p < 0.05.

For each dog of the control group, the coefficient of variation (CV) of each parameter was calculated by dividing the standard deviation by the mean of the absolute values of the parameter recorded during the experiment. Then CVs of the three dogs were averaged, expressed in percentage and presented as mean ± SEM CV%.

Results

Control Dogs

Three control dogs were studied to assess the stability of the electrophysiologic measurements during a prolonged (320, 340 and 405 minutes) chloralose anesthesia. Table 2 summarizes the mean CV of blood pressure and the electrophysiologic data measured during these experiments. The average CV was less than 9% for each measurement.

NAPA and Procainamide Plasma Concentrations

Mean Cps of NAPA and procainamide at 30 minutes and 45 minutes for each of the five infusions are shown in figure 1 and listed in Appendix A. For seven of the 10 pairs of drug concentrations there was no statistically significant difference between the 30- and 45-minute values. Thus, each set of electrophysiologic measurements was made at a time when Cps were reasonably stable. The arithmetic

*Courtesy of Arnar-Stone Pharmaceuticals.
TABLE 2. Mean Coefficient of Variation of Blood Pressure and Electrophysiologic Parameters During Prolonged Anesthesia in the Control Group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Coefficient of Variation (%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>5.5 ± 0.7</td>
<td>4.2-6.5</td>
</tr>
<tr>
<td>SCL</td>
<td>6.3 ± 1.7</td>
<td>3-8.2</td>
</tr>
<tr>
<td>SNRT</td>
<td>8.8 ± 3.6</td>
<td>4.7-16.1</td>
</tr>
<tr>
<td>AH</td>
<td>5.1 ± 0.8</td>
<td>3.7-6.5</td>
</tr>
<tr>
<td>HV</td>
<td>2.8 ± 0.6</td>
<td>1.6-3.7</td>
</tr>
<tr>
<td>QRS</td>
<td>1.05 ± 0.03</td>
<td>1.0-1.1</td>
</tr>
<tr>
<td>QT&lt;sub&gt;v&lt;/sub&gt;</td>
<td>2.8 ± 0.1</td>
<td>2.6-3</td>
</tr>
<tr>
<td>AERP</td>
<td>5.7 ± 0.9</td>
<td>4.3-7.3</td>
</tr>
<tr>
<td>AFRP</td>
<td>4 ± 0.6</td>
<td>3.4-5.2</td>
</tr>
<tr>
<td>NFRP</td>
<td>2.6 ± 0.2</td>
<td>2.1-2.9</td>
</tr>
<tr>
<td>NERP*</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>VERP</td>
<td>6.1 ± 0.8</td>
<td>5.2-7.7</td>
</tr>
<tr>
<td>VFRP</td>
<td>4.4 ± 1</td>
<td>2.4-5.8</td>
</tr>
<tr>
<td>WCL</td>
<td>5 ± 0.6</td>
<td>4.1-6.2</td>
</tr>
</tbody>
</table>

*NERP was recorded consistently in only one dog.

**Abbreviations:** SCL = sinus cycle length; SNRT = sinus node recovery time; AH = interval from the beginning of the atrial depolarization (A) to the beginning of the bundle of His bipolar electrogram (H) measured at 100 mm/sec; HV = His bundle-to-ventricular activation time; QRS = intraventricular conduction times; QT<sub>v</sub> = QT interval; AERP = atrial effective refractory period; AFRP = atrial functional refractory period; NFRP = atrioventricular nodal functional refractory period; VERP = ventricular effective refractory period; VFRP = ventricular functional refractory period; WCL = Wenckebach cycle length; BP = mean arterial blood pressure; inf = infusion.

The mean of Cp at 30 minutes and 45 minutes was calculated for each infusion in each dog and was used to establish all the concentration-response curves. After the end of the fifth infusion, Cps of NAPA and procainamide decreased progressively (fig. 1) with time, but the blood sampling period of time was not long enough to allow accurate comparison of the disposition of the drugs. In the six dogs that received procainamide no measurable acetylation of procainamide was observed during the study. In the eight dogs that received NAPA, a low Cp of procainamide (0.2-0.3 μg/ml) appeared after the first infusion of NAPA and did not increase. This deacetylation process probably occurred during the extraction of the drug from the plasma, because previous experiences in our laboratory have shown that extraction of NAPA from a normal saline solution resulted in a similar level of procainamide.

**Electrophysiologic Results**

The electrophysiologic data are summarized in table 3.

**Sinoatrial Node Automaticity**

The basal values of SCL and SNRT in both groups of dogs were not significantly different. Both NAPA and procainamide showed decreases in SCL and SNRT during the first infusion and progressive increases during subsequent infusions. However, none of the mean slopes of the concentration-response curves of these parameters were significantly different from 0.

**Conduction Times**

The basal AH, HV and QRS intervals were not significantly different between the NAPA and the procainamide groups.

NAPA did not significantly alter AH interval at any Cp. Procainamide initially decreased the AH interval during infusions 1 and 2 then it increased, resulting in a concentration-dependent increase with a mean slope significantly different from 0 (p < 0.01) and from the mean slope of the NAPA group (p < 0.01).

HV conduction time increased progressively during NAPA infusions. The overall change was small, however, and reached a maximum of +12.9 ± 3.3% during the fifth infusion at a Cp of 125 μg/ml. The mean slope of the concentration-dependent increase was significantly different from 0 (p < 0.01) (fig. 2). During procainamide infusions, HV increased progressively to a maximum of +44.3 ± 4.9% during the fifth infusion. The mean slope of the concentration-dependent increase was significantly different from 0 (p < 0.01). The mean slopes of the concentration-response curves of NAPA and procainamide were significantly different (p < 0.01) and procainamide exerted a much more potent effect than NAPA on the conduction in the His-Purkinje system. Two hours after the end of the fifth infusion, HV remained significantly longer than basal for both NAPA (+10.9 ± 2.8%) and procainamide (+31 ± 7%) at a time when Cps were 6.2 ± 2.5 μg/ml and 13.5 ± 0.7 μg/ml, respectively.

The QRS interval increased slightly during the fifth infusion of NAPA but the mean slope of the
Table 3. Changes in Blood Pressure and Electrophysiologic Data During and After (30 minutes, 60 minutes, 120 minutes) Five Successive Bolus Injections and 45-minute Infusions of NAPA and Procainamide

<table>
<thead>
<tr>
<th>N-acetylprocainamide</th>
<th>Basal</th>
<th>1st inf</th>
<th>2nd inf</th>
<th>3rd inf</th>
<th>4th inf</th>
<th>5th inf</th>
<th>30 min</th>
<th>60 min</th>
<th>120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCL (msec)</td>
<td>484.7</td>
<td>435</td>
<td>443.7</td>
<td>446.2</td>
<td>455</td>
<td>463</td>
<td>556</td>
<td>535</td>
<td>410.8</td>
</tr>
<tr>
<td>SNRT (msec)</td>
<td>470.7</td>
<td>465.8</td>
<td>493.6</td>
<td>505.7</td>
<td>511.4</td>
<td>532.1</td>
<td>569</td>
<td>569</td>
<td>500</td>
</tr>
<tr>
<td>AH (msec)</td>
<td>83.7</td>
<td>81.2</td>
<td>91.2</td>
<td>90.7</td>
<td>87.5</td>
<td>89.4</td>
<td>100</td>
<td>33</td>
<td>85.8</td>
</tr>
<tr>
<td>HV (msec)</td>
<td>29.7</td>
<td>29.6</td>
<td>30.7</td>
<td>30.4</td>
<td>31.5</td>
<td>33.6</td>
<td>33</td>
<td>53</td>
<td>29.7</td>
</tr>
<tr>
<td>QRS (msec)</td>
<td>51.9</td>
<td>52.5</td>
<td>53.7</td>
<td>53.1</td>
<td>53.1</td>
<td>55.6</td>
<td>53</td>
<td>53</td>
<td>48.3</td>
</tr>
<tr>
<td>QTc (msec)</td>
<td>298.7</td>
<td>315.9</td>
<td>323.6</td>
<td>335.5</td>
<td>341.5</td>
<td>349.4</td>
<td>33</td>
<td>53</td>
<td>306.7</td>
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<tr>
<td>AERP (msec)</td>
<td>113.7</td>
<td>123.7</td>
<td>127.1</td>
<td>131.2</td>
<td>146.2</td>
<td>167.5</td>
<td>160</td>
<td>160</td>
<td>121</td>
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<tr>
<td>AFRP (msec)</td>
<td>130</td>
<td>136.2</td>
<td>144.3</td>
<td>153.1</td>
<td>165</td>
<td>173.1</td>
<td>168</td>
<td>168</td>
<td>126.7</td>
</tr>
<tr>
<td>NFRP (msec)</td>
<td>212.1</td>
<td>205.8</td>
<td>229.2</td>
<td>230.2</td>
<td>234.8</td>
<td>238.8</td>
<td>235</td>
<td>235</td>
<td>215.8</td>
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<tr>
<td>VERP (msec)</td>
<td>150</td>
<td>156.7</td>
<td>164.2</td>
<td>171.7</td>
<td>185.8</td>
<td>186.7</td>
<td>180</td>
<td>180</td>
<td>161.7</td>
</tr>
<tr>
<td>VFRP (msec)</td>
<td>184.9</td>
<td>173.3</td>
<td>176.2</td>
<td>183.3</td>
<td>185.8</td>
<td>190.7</td>
<td>193</td>
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<td>191.7</td>
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<td>WCL (mm Hg)</td>
<td>89.7</td>
<td>84.3</td>
<td>88.6</td>
<td>93.2</td>
<td>84.8</td>
<td>87.6</td>
<td>88</td>
<td>88</td>
<td>84.3</td>
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<tr>
<td>BP</td>
<td>80.0</td>
<td>74.5</td>
<td>80.6</td>
<td>83.6</td>
<td>77.2</td>
<td>84.5</td>
<td>88</td>
<td>88</td>
<td>74.5</td>
</tr>
</tbody>
</table>

Abbreviations: see table 2.

The concentration-response curve was not significantly different from 0 (fig. 3). During the third, fourth, and fifth infusions of procainamide, QRS interval increased and the mean slope of the concentration-response curve was significantly different from 0 ($p < 0.01$) and from the slope of the NAPA group ($p < 0.01$).

**QTc Interval**

Basal values of QTc were not significantly different between the NAPA and procainamide groups. Both drugs produced a concentration-dependent increase of the QTc interval, with mean slopes significantly different from 0 ($p < 0.001$ for NAPA, and $p < 0.001$ for procainamide) (fig. 4). Procainamide and NAPA had a similar potenti in increasing the QTc interval duration, and the slopes of their concentration-response curves were not significantly different. After the end of the last infusion, QTc interval continued to increase for NAPA and reached a peak value at 30 minutes postinfusion. At this time in the procainamide group, QTc had returned to basal values.

**Atrial Refractory Periods**

The basal values of AERP and AFRP were not significantly different in both groups of dogs. NAPA and procainamide produced a parallel concentration-dependent increase of AERP with mean slopes significantly different from 0 ($p < 0.001$ for NAPA and $p < 0.05$ for procainamide) (fig. 5). Similarly, both drugs produced a concentration-dependent increase of AFRP with mean slopes significantly different from 0 ($p < 0.05$ for NAPA and $p < 0.01$ for procainamide).
different from 0 ($p < 0.001$ for NAPA and $p < 0.05$ for procainamide). Although there was no significant difference between mean slopes of the two groups for AERP and AFRP, procainamide seemed to be more potent than NAPA.

**AV Nodal Refractory Periods**

The NFRP was measured in seven dogs during NAPA infusions and in six dogs during procainamide infusions. Basal values of NFRP were not significantly different in both groups of dogs. Both drugs produced a concentration-dependent increase of the NFRP duration with mean slopes significantly different from 0 ($p < 0.05$ for NAPA and $p < 0.001$ for procainamide). Procainamide was more effective than NAPA on NFRP duration. There was also a significant difference in mean slopes of the two groups ($p < 0.05$) (fig. 6).

Because atrial refractoriness was often reached first, NERP was consistently recorded in only one dog of the NAPA group and two dogs of the procainamide, precluding any accurate comparison. NERP duration increased by a maximum 68.7% after the fifth infusion of NAPA (Cp NAPA 142.7 µg/ml), and the slope of the concentration-response curve was 20.2 in one dog. In the two dogs of procainamide group, the increase of NERP reached a maximum of 13.3% and 40% after the fifth infusion of procainamide (Cp 29.1 and 40.8 µg/ml, respectively) and the slopes of the concentration-response curves were 19.8 and 28.3.

**Ventricular Refractory Periods**

Basal values of VERP and VFRP were not significantly different for the two groups. NAPA in-
increased VERP progressively to a maximum of +15.2 ± 5.6% by the third infusion, but the effect plateaued during the two subsequent infusions (fig. 7). Because we did not appear to be operating on the log-linear portion of the concentration-response curve, but seemed to have described the final portion of the sigmoid curve, we did not attempt to perform a log-linear correlation between VERP and the five Cps NAPA. If one considers only the three first concentrations of NAPA, NAPA produced a concentration-dependent increase of VERP with a mean slope significantly different from 0 (p < 0.05). The maximum increase of VERP (+27.5 ± 5.5%) occurred 30 minutes after the end of the fifth infusion of NAPA. Procainamide produced a concentration-dependent increase of VERP with a mean slope significantly different from 0 (p < 0.01) After the last infusion of procainamide, VERP duration decreased promptly. To allow comparison with the effects of NAPA, the slope of the concentration-response curve was calculated for the three concentrations of procainamide equivalent to the three first concentrations of NAPA (range 7.5–32 μg/ml). For these three concentrations, procainamide produced a significant concentration-dependent increase of VERP (p = 0.01), and NAPA and procainamide exerted similar effects.

VFRP increased during NAPA infusions in a concentration-dependent manner (p < 0.05). As with VERP duration, the maximum increase of VFRP was reached after the last NAPA infusion. Procainamide produced a concentration-dependent increase of VFRP (p < 0.001) that was highest during the fifth infusion. Mean slopes of the concentration-response curves for NAPA and procainamide were significantly different (p < 0.05). At a higher Cp, procainamide exerts a more potent effect than NAPA on VFRP duration.

The Wenckebach Phenomenon Cycle Length

The basal values of WCL were not significantly different between the NAPA and procainamide groups. Both drugs produced an equivalent concentration-dependent increase in WCL (p < 0.01 for NAPA and p < 0.01 for procainamide) and the potency and slopes of their concentration-response curves were not significantly different (fig. 8). However, after the end of the last infusion of NAPA, WCL continued to increase to a maximum of 35 ± 7.5% at 120 minutes. In the procainamide group WCL decreased after the fifth infusion.

Blood Pressure

Basal values of blood pressure were not significantly different between the groups. Neither NAPA nor procainamide caused a statistically significant change in blood pressure measured at 30 minutes of each of the five infusions.

Discussion

Procainamide has been used for many years to treat arrhythmias. However, the high incidence of immunologic reactions limits the long-term use of procainamide as an antiarrhythmic agent. NAPA, the principal metabolite of procainamide in man, may not have this toxicity and may become an alternative drug inasmuch as it has antiarrhythmic activity in both animal models and patients. Our canine electrophysiologic comparative study of procainamide and NAPA may be useful to compare their cardiac effects and to delineate the possible mechanism of action of NAPA.

Sinus Automaticity

Data are conflicting regarding the effects of procainamide and NAPA on the heart rate. Procainamide has been reported to decrease heart rate, to increase it or to produce no significant
Bagwell et al.\textsuperscript{10} and Amlie et al.\textsuperscript{14} found a decrease of the heart rate after injection of both procainamide and NAPA in pentobarbital-anesthetized dogs. Using isolated rat atria, Refsum et al.\textsuperscript{13} showed a difference between procainamide and NAPA in their potency to increase (NAPA) or to decrease (procainamide) the spontaneous atrial rate.

Our study in chloralose-anesthetized dogs showed no significant effect on either heart rate or SNRT. Although the changes did not reach statistical significance, both drugs slightly increased heart rate and shortened SNRT at lower concentrations and slowed heart rate and prolonged SNRT at higher concentrations. This trend was most marked for procainamide. The conflicting data in published studies may result from a dual action of these compounds. One might postulate that net effect of the drugs on the sinus node may be the result of predominant vagolytic action\textsuperscript{32} at lower drug concentrations and overriding direct depressant actions of higher concentrations.

Conduction Times

Although the effects of procainamide and NAPA on the intracardiac conduction times depend on the portion of the conduction pathway measured, overall, procainamide seems to exert a much more potent effect than NAPA.

1) NAPA did not increase significantly the atrio-nodal conduction time always measured at the same driven atrial rate, while procainamide produced a concentration-dependent increase. The lack of effect of NAPA on AH conduction time is consistent with the findings of Amlie et al.\textsuperscript{14} The data are conflicting with regard to the effect of procainamide both in dogs or in humans; some authors finding a negative dromotropic effect,\textsuperscript{14, 33} some a positive dromotropic effect\textsuperscript{28} and others no significant effect.\textsuperscript{29-31} Once again, mixed vagolytic and direct effects could explain these discrepancies.

2) In our study procainamide prolonged the His-Purkinje and the intraventricular conduction times in a log-linear relationship with Cp. These data are consistent with the data in anesthetized dogs,\textsuperscript{14, 25, 33} in conscious dogs\textsuperscript{24} and in patients.\textsuperscript{29-31} This is also consistent with the effects of procainamide on the electrophysiologic properties of isolated canine Purkinje fibers: a decrease of conduction velocity and of the amplitude and the maximal rate of rise of phase 0 of the action potential.\textsuperscript{27}

The effects of NAPA on HV conduction times were different from those of procainamide. NAPA produced a significant concentration-dependent increase of HV, but compared with the effects of procainamide, the latter exerted a much more important effect. The maximum NAPA-induced increase in HV occurred during the fifth infusion, when the Cp was around 125 \( \mu \)g/ml. Amlie et al.\textsuperscript{14} investigated the effects of NAPA only to a maximum Cp of 30 \( \mu \)g/ml and did not find any significant change of HV. Our data are consistent with these results because at this lower Cp, the increase of HV in our experiment was small and not significant. The effect of NAPA on the intraventricular conduction time was also much different from that of procainamide. This minimal effect of NAPA on QRS duration and its very weak negative dromotropic effect on His-Purkinje conduction make NAPA different from procainamide. These results are in agreement with the recent findings of Dangman and Hoffman\textsuperscript{34} who showed that in canine cardiac Purkinje fibers, NAPA exerted no significant change of the maximal velocity of the upstroke (phase 0) of the action potential at concentrations of 20 and 40 \( \mu \)g/ml.

Cardiac Refractory Periods and \( QT_c \), Interval

Both procainamide and NAPA increased the AERP and AFRP in relation to the log of the Cp. These results confirmed the data of Amlie et al.\textsuperscript{14} in anesthetized dogs and those of Minchin et al.\textsuperscript{11} on isolated rabbit atria and those of Refsum et al.\textsuperscript{13} on isolated rat atria. Our results are similar to these later studies in that we found NAPA was slightly less effective than procainamide in increasing atrial refractory periods. Procainamide had previously been shown to increase the duration of atrial refractory periods both in anesthetized dogs\textsuperscript{29-31} and in patients.\textsuperscript{29, 31}

The AV nodal refractory periods were increased both by procainamide and NAPA and both drugs were equipotent for increasing the Wenckebach cycle length. The effects on the NFRP are in agreement with those of Amlie et al.,\textsuperscript{14} but the studies of Josephson et al.\textsuperscript{31} and Ogunkelu et al.\textsuperscript{29} showing no significant effect of procainamide on NFRP and a decrease of NERP are in conflict with our results. However, these two studies were done in patients, where the neural control of the AV nodal conduction time may be different from that in anesthetized dogs.

Both procainamide and NAPA increased VFRP, VERP, and \( QT_c \). The increase of ventricular refractory periods by procainamide are in agreement with previous studies in patients,\textsuperscript{29, 31} and in canine Purkinje fiber studies in which Rosen et al.\textsuperscript{27} have shown that procainamide increases the action potential duration and the VERP. Bagwell et al.\textsuperscript{10} also showed significant increase of the VFRP and of the repolarization time with procainamide and NAPA in canine His-Purkinje preparations. Amlie et al.\textsuperscript{14} have also shown that both drugs increased VFRP and VERP durations to almost the same extent. Dangman and Hoffman\textsuperscript{34} showed that NAPA increased the action potential duration of canine Purkinje fibers in a dose-dependent manner. These data are in agreement with our data showing the same potency of NAPA and procainamide in increasing the \( QT_c \) interval duration in a log-Cp-related way.

Arterial Pressure

Neither procainamide nor NAPA significantly modified arterial pressure in our experiments. This lack of effect of procainamide is in agreement with the results of Rosen et al.\textsuperscript{27} in anesthetized dogs, of O'Rourke et al.\textsuperscript{28} and Mandel et al.\textsuperscript{26} in conscious
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dogs, and of Ogunkelu et al. 29 in patients. However, in
pentobarbital-anaesthetized dogs, Bagwell et al. 10
showed a difference between procainamide, which
decreased blood pressure, and NAPA, which did not
cause any significant modification. Woske et al. 33
showed that in anaesthetized dogs procainamide caused
an initial fall in blood pressure that was related more
closely to the speed with which the drug was ad-
ministered than to the total amount of drug injected.
This fact may explain why Amlie et al. 14 observed a
transient fall in systolic blood pressure after an
intravenous injection of procainamide or NAPA with a
return of blood pressure to predrug values 30–40
minutes later and why in our experiment, after 30
minutes of a constant intravenous infusion of
procainamide or NAPA, there was no significant
change of blood pressure. The vasodilator effect of
procainamide, which may be caused by an inhibition
of ganglionic transmission, 35 may have been transient
after each bolus injection and may have disappeared
by the time our recordings of the arterial pressure
were performed.

Our postinfusion measurements indicate that there
may be some pharmacodynamic differences between
NAPA and procainamide with regard to their elec-
trophysiologic effects. NAPA has a longer half-life
than procainamide 1, 7, 21 and in our study, a higher
concentration of NAPA was present at the end of the
last infusion than the corresponding concentration
of procainamide. These two factors may explain why
we observed a longer effect of NAPA than procainamide
on QTc, WCL and the duration of the refractory
periods. However, they do not explain the maximum
effects of NAPA on QTc, WCL, VERP, and VFRP
after the end of the last infusion. Perhaps NAPA does
not reach some sites of action as rapidly as pro-
cainamide.

It is extremely difficult to extrapolate from our
results in anesthetized dogs to the possible mechanism
of action of these antiarrhythmic drugs in man.
NAPA and procainamide probably exert close or
similar actions on cardiac refractoriness while they
show striking differences in their effects on intracar-
diac conduction. Procainamide appears to be more
potent in slowing conduction in the different portions
of the conduction pathway, while the effects of NAPA
remain limited or nonsignificant. If slowing of con-
duction is a mechanism of procainamide-induced suppres-
sion of reentry, the antiarrhythmic effects of NAPA
would be weaker than those of procainamide. This
speculation does not include other possible mech-
anisms of antiarrhythmic effect dependent on the
effects of the drugs on refractoriness or excitability.
However, our animal study may help to explain the
apparent difference in therapeutic Cp between NAPA
and procainamide. The generally accepted Cp for
procainamide is 4–8 μg/ml 46 whereas a recent study of
Atkinson et al. 12 suggests an average Cp of 11
μg/ml of NAPA is required to suppress ventricular
premature complexes.

In conclusion, NAPA may have different elec-
trophysiologic properties from its parent compound,
procainamide. At a clinically relevant Cp NAPA has
almost no effect on His-Purkinje and intraventricular
conduction times and a less important effect on the
atrial and AV nodal refractory periods. These data
suggest that in addition to their differences in phar-
macokinetics, the drugs may have different anti-
arrhythmic mechanisms of action, different effective
antiarrhythmic concentrations and different electrical
cardiac toxicities.

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APPENDIX A. Mean Plasma Concentrations (Cp) of Procainamide and N-acetylprocainamide (mg/ml) at 30 and 45 Minutes of Each of the Five Infusions

<table>
<thead>
<tr>
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<th>1</th>
<th>2</th>
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</thead>
<tbody>
<tr>
<td>N-acetylprocainamide (n = 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cp 30 min</td>
<td>8.8 ± 0.38</td>
<td>15.84 ± 0.5</td>
<td>32.4 ± 1.4</td>
<td>64.1 ± 3.2</td>
<td>126 ± 6.4</td>
</tr>
<tr>
<td>Cp 45 min</td>
<td>7.61 ± 0.26</td>
<td>15.2 ± 0.9</td>
<td>29.9 ± 1.3</td>
<td>60.2 ± 2.6</td>
<td>124 ± 8</td>
</tr>
<tr>
<td>Cp</td>
<td>8.21 ± 0.3</td>
<td>15.52 ± 0.7</td>
<td>31.1 ± 1.3</td>
<td>62.3 ± 2.9</td>
<td>124.94 ± 7</td>
</tr>
<tr>
<td>Procainamide (n = 6)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Cp 30 min</td>
<td>1.16 ± 0.97</td>
<td>3.3 ± 0.29</td>
<td>7.6 ± 0.48</td>
<td>15.06 ± 1.15</td>
<td>32 ± 2.6</td>
</tr>
<tr>
<td>Cp 45 min</td>
<td>1.72 ± 0.11</td>
<td>3.48 ± 0.25</td>
<td>7.5 ± 0.5</td>
<td>13.9 ± 1.17</td>
<td>32.1 ± 2.2</td>
</tr>
<tr>
<td>Cp</td>
<td>1.79 ± 0.1</td>
<td>3.42 ± 0.27</td>
<td>7.57 ± 0.5</td>
<td>14.5 ± 1.12</td>
<td>32.09 ± 2.3</td>
</tr>
</tbody>
</table>

The arithmetic mean of Cp at 30 minutes and Cp at 45 minutes was calculated for each dog (Cp) and averaged.
Electrophysiologic comparative study of procainamide and N-acetylprocainamide in anesthetized dogs: concentration-response relationships.
P Jaillon and R A Winkle

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