Comparative Cardiac Effects of Three Hepatobiliary Radiopharmacologicals in the Dog: Concise Communication

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Three hepatobiliary agents with an acetanilide-imidoacetic-acid moiety resembling that in lidocaine were investigated for their possible effects on contractility and conductivity in the heart and on arterial pressure and aortic blood flow. This was done in the light of lidocaine's numerous cardiac side effects. HIDA, BIDA, and DIPA, each with traces of decayed Tc-99m, were injected i.v. into anesthetized dogs with an A-V block, and their effects on the above parameters were followed until control levels were reestablished. Whereas lidocaine raises the diastolic threshold and prolongs the refractory period, the three agents tested do not prolong myocardial conductivity. Both HIDA and BIDA have an effect similar to that of lidocaine, but DIPA has no effect on the latter two parameters. Moreover, whereas lidocaine depresses myocardial contractility, blood pressure, and blood flow, HIDA has a less prominent effect on these parameters, and neither BIDA nor DIPA has any such effect. It is concluded that even though the effect of HIDA on the heart is milder than that of lidocaine, the effects of both BIDA and DIPA are even less pronounced, and they are less likely to cause cardiac side effects when similar doses are administered during nuclear medicine procedures.

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Since the introduction of Tc-99m 2,6,dimethylacetanilideiminodiacetic acid (Tc-99m HIDA) as an hepatobiliary agent in 1975 (*1,2*), other iminodiacetic acid (IDA) derivatives have been developed and tested clinically for that purpose (*3–5*). Among these, Tc-99m p-n-butylacetanilide-IDA (Tc-99m BIDA), and lately Tc-99m 2,6-di-isopropylacetanilide-IDA (Tc-99m DIPA) have been widely used for the diagnosis of hepatobiliary extraction efficiency and transit time. The structural common denominator of these three chemicals is an acetanilide-IDA moiety, which is the same as that in lidocaine (Fig. 1). Lidocaine (Xylocaine), a common antiarrhythmic agent, has profound cardiovascular effects: at a dose of 1–1.5 mg/kg i.v. it suppresses the automaticity of the Purkinje fibers, abbreviates the duration of the action potential in both Purkinje and muscle fibers, and shortens the effective refractory periods of the Purkinje fibers. At doses of 2–3 mg/kg it causes little change in A-V conduction time, contractility, intraventricular conduction, or heart rate (*6*). As all three agents mentioned are frequently applied in nuclear medicine, with similar and overlapping indications (*7,8*), we considered it essential to investigate their possible side effects on cardiovascular function.

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MATERIALS AND METHODS

Thirty-six fasted mongrel dogs (20–25 kg) were used. Each was anesthetized with 30 mg/kg i.v. sodium pentobarbital, and the chest was opened, under positive-

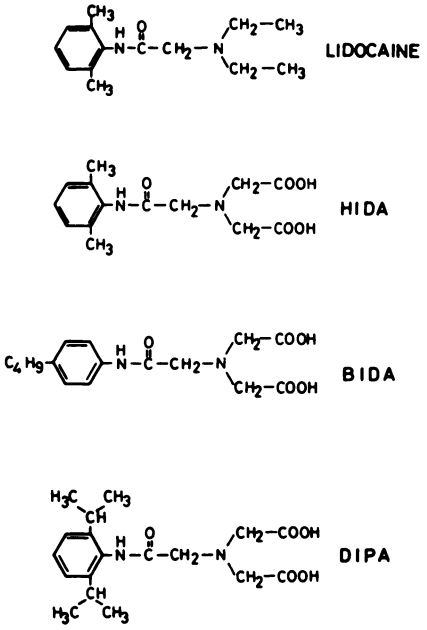

FIG. 1. Structural resemblances between lidocaine and three acetanilide-IDA derivatives tested for their cardiac side effects.

pressure respiration, by a longitudinal sternal split. During temporary caval obstruction, complete A-V block was produced by electrocoagulation of the A-V region under direct vision. Rhythmic cathodal ventricular stimulation (S_1) was applied through a hook electrode attached to the apex of the right ventricle, with a 2 × 4 cm metal plate inserted under the epigastric skin. These unipolar ventricular stimuli were delivered by a stimulator* at a rate of 100/min, with an intensity of 1-2 mA and duration 2 msec. Right-ventricular isometric tension was measured with a strain-gauge arch,† and the myocardial tension at the site of the ventricular stimulation was monitored by a miniature strain-gauge arch developed in our laboratory (*9*). The latter measured the force exerted on two needles inserted 2 mm apart in the ventricular wall, the muscle being stretched between them to obtain isometric tension. With a variable post-S_1 delay interval, another stimulus (S_2) was given through one of the miniature strain-gauge needles and another metal plate, with intensity 0.2-5.5 mA and duration 2 msec. The intensities of the S_2 stimuli were measured by the voltage difference across a 10-Ω resistor connected in series with the stimulating electrode and displayed on a Tektronics storage oscilloscope. The sweep of the scope was triggered by the S_1 stimulus and the S_1-S_2 delay was measured by the calibrated time sweep of the scope.

The first derivative of the right-ventricular tension (dT/dt) was monitored. Blood flow (ml/min) was measured by an electromagnetic flow-meter‡ with a probe placed on the base of the aorta. Systemic blood pressure was recorded through a pressure transducer connected to an intra-aortic catheter. Lead II surface ECG was obtained throughout the experiment. All parameters were recorded on a thermal recorder. Serum pH, Na^+, and K^+ values were determined at the beginning of the experiment and twice during its course.

Two types of threshold curve were recorded: the upper limit T_U and the lower limit T_L of threshold (*10*). T_U was designated as the smallest current level sufficient to induce consistent depolarization by S_2 stimuli at various post-S_1 intervals from the end of the absolute refractory period into diastole. T_L was defined as the current just insufficient to evoke depolarization at a given interval following the driven beat, after a train of extrasystoles. Repeated determinations of the T_U and T_L curves within 60 min resulted in no significant alterations in these values (Fig. 2). Differences between groups of points were determined by Student's t-test, and a shift of the curve was considered "mild," "significant," or "highly significant" ("profound") when 4, 5, or 6 groups of points on a six-point curve were different ($p < 0.05$) from their corresponding control values.

Myocardial conduction was measured by simultaneous recording of isometric tension from the right ventricle's free wall by the strain-gauge arch, as well as by the miniature strain gauge (*11,12*). The time delay in the mechanical response at the site of the electrical stimulation, compared with the rest of the ventricle, was considered to be due to conduction delay. All the above measurements were obtained in all 36 dogs, nine of which were studied for each drug administered. In order to eliminate the natural variability between dogs, each was considered a control for itself during its specific treatment.

HIDA, BIDA, or DIPA (Fig. 1) kits were dissolved before injection in decayed Tc-99m generator eluate and

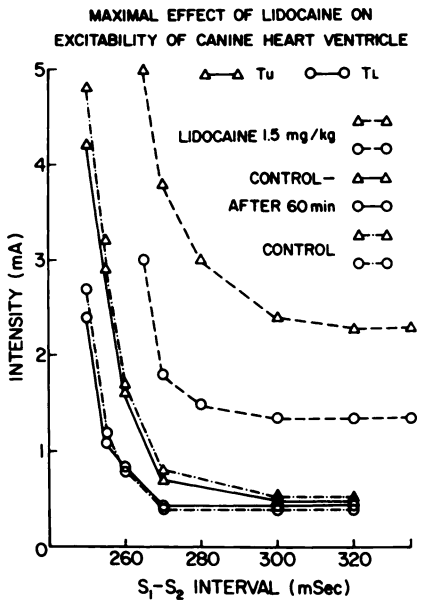

FIG. 2. Strength-interval curves (T_U, T_L) from canine heart ventricle after 60 min without intervention. Note lack of difference from control, and displacements of curves after 1.5 mg/kg lidocaine.

were given as an i.v. bolus. As the diagnostic dose of the three radiopharmaceuticals is about 0.1 mg/kg of base, we chose this and a ten-fold higher dose. The dose of lidocaine was 1.5 mg/kg, which is comparable with that administered clinically for treatment of cardiac arrhythmias.

Since the kits were dissolved in decayed Tc-99m solutions, it is obvious that the actual concentration of the Tc-99m species injected is extremely low. Therefore, the pharmacological effects noted in this paper are attributed to the great excess of the unreacted ligand, and the drugs are refered to in the text as HIDA, BIDA, and DIPA solutions rather than Tc-99m HIDA, etc.

RESULTS

During all of our experiments, systolic blood pressure remained constant, within a range of not more than 10% during any single experiment. Serum levels of Na^+, K^+, and pH were stable and within physiological limits.

Excitability. Lidocaine 1.5 mg/kg caused highly significant displacement of the T_U and T_L curves upward and to the right in all nine dogs examined (Fig. 2). A typical strength-interval curve for HIDA is presented in Fig. 3. Whereas a dose of 0.1 mg/kg caused a mild upward and rightward shift of the T_U and T_L curves compared with lidocaine in four of the nine dogs examined, the effect of 1 mg/kg in seven of the dogs was more profound, even though less marked than that of lidocaine.

Figure 4 illustrates a typical strength-interval curve for BIDA. A dose of 0.1 mg/kg caused a mild change in only two of the nine dogs tested, with a slight prolongation of the refractory period (displacement to the right) and rise in the systolic threshold (upward displacement). After a 1.0 mg/kg bolus the changes were much more profound and were significant in five of the dogs so treated, but they were still less distinct than those after lidocaine or HIDA. No significant changes in either of the two curves were noticed after administration of 0.1 or 1.0 mg/kg DIPA to nine dogs (Fig. 5). In all cases the strength-interval curves returned to pretreatment levels within 40 min after administration of the drug.

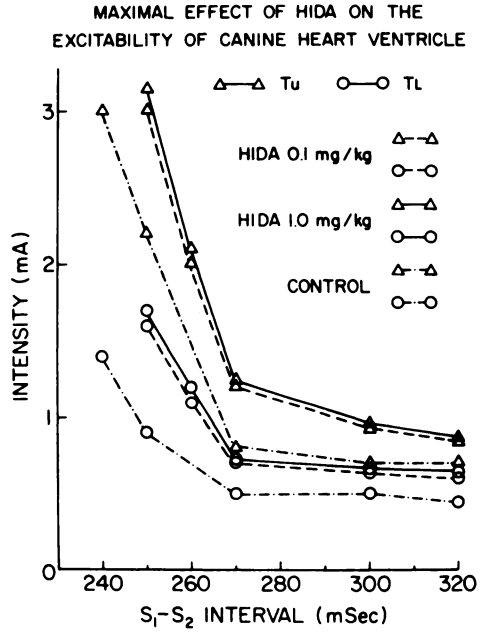

FIG. 3. Typical strength-interval curves from canine heart ventricle, showing rightward and upward shift of curves after administration of HIDA.

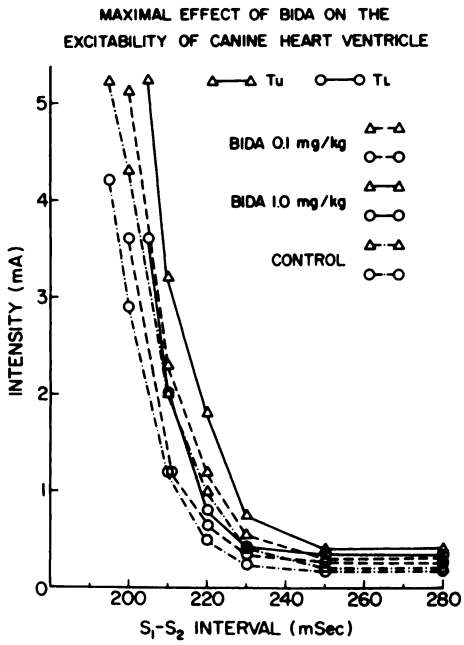

FIG. 4. Typical strength-interval curves from canine heart ventricle, showing minimal effect of BIDA.

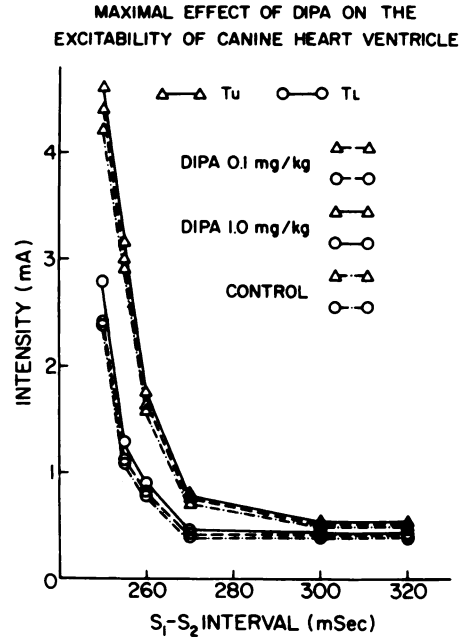

FIG. 5. Typical strength-interval curves from canine heart ventricle after administration of DIPA. Note drug's lack of effect.

Myocardial conduction. Myocardial conduction is measured as the time difference in the occurrence of mechanical response at the site of the electrical stimulation compared with the rest of the ventricle (*11,12*). All four drugs tested apparently produced slightly slowed conduction in the myocardium, but this effect was not significant.

Contractility. Changes in contractility were demonstrated in our studies by a drop in the peak isometric tension, as recorded by a strain-gauge arch and by the changes in the first derivative of the tension (dT/dt), recorded before and after administration of each drug. A significant drop in peak tension was obtained in our studies only after administration of 1.5 mg/kg lidocaine ($p < 0.1$) and 1.0 mg/kg HIDA ($p < 0.05$), the mean decreases in peak tension being 21.7 ± 3.5% and 19.4 ± 3.1%, respectively. The highly significant decrease (40%) in peak tension caused by HIDA at 1 mg/kg is illustrated in Fig. 6. The decreases in peak tension after BIDA and DIPA at 1 mg/kg were measurable (6.9 ± 1.9% and 8.2 ± 3.3%, respectively) but not significant.

The decrease in dT/dt was demonstrated after administration of all four drugs, but was significant only after lidocaine at 1.5 mg/kg (30.2 ± 2.9%, $p < 0.1$) and HIDA at 1 mg/kg (25.8 ± 5.7%, $p < 0.01$). All changes observed in myocardial tension returned to control levels within 10 min after administration of the drug.

Blood pressure and blood flow. Systolic blood pressure appeared slightly reduced after injection of any of the four drugs, but in no instance was it significant. A reduction in aortic blood flow was also noticed with all drugs, with significant differences after lidocaine at 1.5 mg/kg (14.3 ±3.8%) and HIDA at 1 mg/kg (12.7 ± 3.2%) ($p < 0.05$).

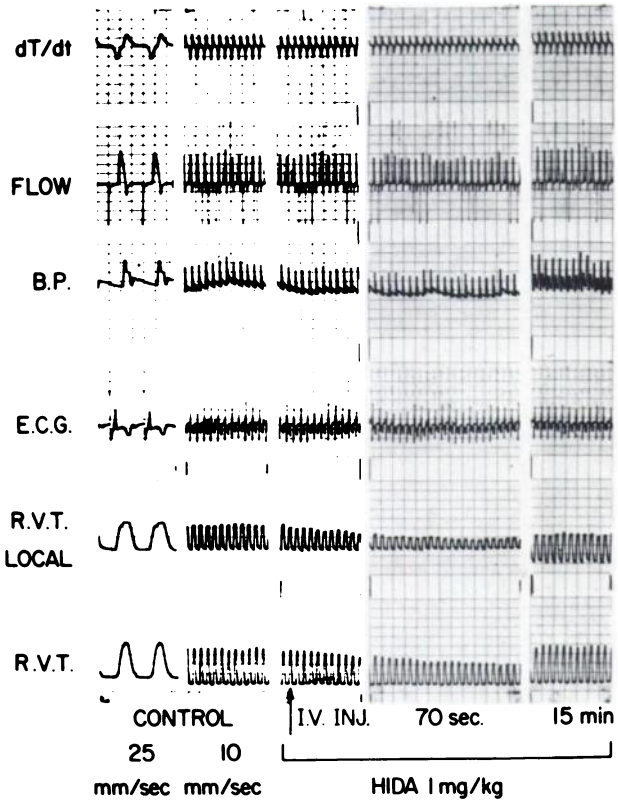

FIG. 6. Records showing that cardiac parameters tested returned to normal levels within 15 min after HIDA administration.

DISCUSSION

The structure-activity relationship of some IDA compounds was studied by Subramanian et al. (*5*), who suggested that as the lipophilicity of the substituted group increased its biliary excretion also increased, and that as the substituted group was changed in the 2,6 positions from methyl to isopropyl, the 15-min urinary excretion decreased and the concentration in the liver increased.

In a later publication Firnau (*13*) explored the structural requirements for substances that serve as hepatobiliary agents, and suggested that only organic anions with a molecular weight of 300–1000 would be able to pass quickly through the liver and permit imaging of the gallbladder and bile ducts. In a recent publication Harvey et al. (*14*) suggested that HIDA is transported through the hepatocytes by a carrier-mediated organic-anion pathway, and that new anionic hepatobiliary agents should be capable of displacing endogenous bilirubin from its transport binding sites. Since the cardiotoxic effects apparently decrease with an increase in lipophilicity, it can be reconfirmed that the dominant pathway of the drug's uptake in the heart is the anionic one (*14,15*) and that there is an apparent increase in lipophilicity from HIDA to DIPA, with retainment of the basic structure of the molecule. In this group of IDA derivatives, the lesser lipophilic substances favor renal clearance, and therefore their cardiotoxic binding and other effects are significantly stronger.

In our study we found that lidocaine in large doses may cause marked effects on the nervous and cardiovascular systems, leading to respiratory depression and arrest as well as to hypotension, bradycardia, cardiac arrest, and psychomotor restlessness (*16*). Since radiopharmaceuticals with the same structural moiety are currently used as hepatobiliary agents, our investigation compared the effects of those radiopharmacological agents on various cardiac parameters.

Lidocaine is known to reduce automaticity, prolong the effective refractory period and raise the diastolic threshold at normal serum K^+ concentrations (*17–22*), and this was confirmed in our study. Lidocaine prolonged the refractory period (rightward displacement of the strength-interval curve) and raised the diastolic threshold (upward displacement of the curve). We also noticed that HIDA has the same qualitative effects at 1 mg/kg as lidocaine at 1.5 mg/kg, but in general the severity of the HIDA effects was less profound. The effects of

BIDA were shown to be milder at 1 mg/kg, while DIPA exerted no measurable effects on the parameters studied.

The effect of lidocaine on myocardial conductivity is somewhat controversial (*22,23*), with minimal or no effect on conduction time. The present study suggests that none of the four drugs tested has any significant slowing effect on myocardial conduction time. Hence lidocaine has some negative inotropic effects (*22,24–26*) and in this study caused significant depression of both contractility (myocardial isometric tension and its first derivative) and hemodynamics (aortic blood flow and systolic blood pressure). The effect of HIDA on these parameters was profound, but the effects of both BIDA and DIPA were less noticeable.

In conclusion, it seems that an i.v. bolus of 1 mg/kg HIDA preparation has effects on the heart similar to those of lidocaine, and thus it should be given at the lowest possible dose when administered as a tracer for scanning of the hepatobiliary system. It is demonstrated hereby that DIPA and BIDA exert no ill effects on the cardiac functions, even if given at a dose ten times that required for radiopharmaceutical scanning. It is suggested, therefore, that DIPA should be preferred over HIDA wherever possible for hepatobiliary scanning in patients with cardiac malfunction.

FOOTNOTES

* Grass S-88.
† Walton-Brodie.
‡ Statham SP 2200.

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