Cardiovascular and Respiratory Effects of Antiarrhythmic Drugs on Conscious Beagles

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HASHIMOTO, K., SHIBUYA, T. and IMAI, S. *Cardiovascular and Respiratory Effects of Antiarrhythmic Drugs on Conscious Beagles*. Tohoku J. exp. Med., 1985, **145** (4), 359-367 — Cardiovascular effects of antiarrhythmic drugs and their effects on the respiratory rate were examined in conscious beagles. Disopyramide, 1.5 mg/kg i.v., increased the blood pressure and decreased the heart rate, but higher dose of 5 mg/kg i.v. increased both. Disopyramide showed no central nervous side effects. Procainamide, 20 and 60 mg/kg i.v., increased the blood pressure and heart rate without changing the respiratory rate. A higher dose (60 mg/kg i.v.) of procainamide induced vomiting. Lidocaine, 2 and 6 mg/kg i.v., and phenytoin, 3 and 10 mg/kg i.v., simultaneously increased the blood pressure, heart rate and respiratory rate accompanied by excitement, and with a higher dose (6 mg/kg i.v.) of lidocaine, by convulsions. Verapamil, 0.1 and 0.3 mg/kg i.v., induced tachycardia without serious neurological effects. In conscious healthy dogs cardiovascular depressant actions of antiarrhythmic drugs could only rarely be observed. ——— Conscious dog; blood pressure; heart rate; respiratory rate; antiarrhythmic drugs.

It is well known that antiarrhythmic drugs have cardiovascular, autonomic and central nervous side effects (Kumana and Hamer 1979; Bigger and Hoffman 1980). Recently we reported antiarrhythmic and cardiovascular effects of antiarrhythmic drugs using three canine ventricular arrhythmia models. They were the two-stage coronary ligation arrhythmia in conscious beagles (Hashimoto et al. 1982, 1983), digitalis-induced arrhythmia in pentobarbital anesthetized dogs (Hashimoto et al. 1983) and adrenaline-induced arrhythmia in halothane anesthetized dogs (Hashimoto et al. 1983; Shibuya et al. 1983). Our previous studies are summarized in the left panel of Table 1. Dogs used for the arrhythmia models are too far from their normal conscious state to allow some side effects of drugs to be observed. We designed the present experiments to compare effects of the commonly used five antiarrhythmic drugs on the blood pressure and heart rate, simultaneously examining the neurological side effects on normal conscious

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beagles without arrhythmia. Since evaluation of drug effects on the central nervous system in the conscious animal is difficult, we recorded the changes in the respiratory rate. It is expected that the central stimulant drugs increase respiration, while depressants have the opposite effect. We chose disopyramide, procainamide, lidocaine, phenytoin and verapamil, which were effective in suppressing some or all of the canine ventricular arrhythmia models (Hashimoto et al. 1982, 1983; Shibuya et al. 1983).

METHODS

Eight male beagle dogs, weighing 7–11 kg, were used. They were anesthetized with sodium thiopental, 30 mg/kg i.v., and an arterial and a venous cannula were inserted through the femoral artery and vein, and the other ends of the cannulae were led subcutaneously to a hole in the skin of the back neck. Experiments were done several days after this operation.

The animal was placed in a silent and air-conditioned room. Lead II ECG was recorded using telemetry systems (Nihon Kohden, ZR-601G and ZB-141G) and the blood pressure was also recorded using a telemetry system (Nishimu) (Nonaka and Ueno 1980) and the heart rate was recorded using a cardi tachograph (Nihon Kohden, AT-601G) triggered by the R wave of the ECG. The respiratory rate was recorded using a thorax movement pick-up (Nihon Kohden, TR-601T and AA-601H) and a respiratory rate meter (Nihon Kohden, IR-612P). Drugs were injected through the venous cannula with a long extension tube. Animals were given two injections of different doses in one day and similar experiments using other drugs were done every other day.

Drugs used were solutions in ampoules of disopyramide phosphate (50 mg/5 ml, Nippon Roussel), procainamide hydrochloride (200 mg/2 ml, Daiichi), lidocaine hydrochloride (100 mg/5 ml, Fujisawa), phenytoin (250 mg/5 ml, Dainippon) and verapamil hydrochloride (5 mg/2 ml, Eisai).

The data in the figures are expressed in terms of mean $\pm$ s.d. and the statistical significance was examined using the Student *t*-test for paired data, comparing the values after injection with the 0 time values.

RESULTS

After installing the recording instruments, 30 min to 2 hr were necessary before starting experiments to obtain a stable state in the dog which was conscious and quiet. The mean values of the blood pressure, heart rate and respiratory rate were about 100 mmHg, 100 beats/min and 30/min, respectively, as shown in the control values in Figs. 1–5. Injection of 0.9% NaCl solution up to 10 ml did not affect any of these parameters until at least 30 min after injection.

Disopyramide (Fig. 1)

Disopyramide 3 to 5 mg/kg i.v. was effective in suppressing arrhythmias produced by digitalis, coronary ligation and adrenaline in dogs in our previous studies (Hashimoto et al. 1982, 1983; Shibuya et al. 1983), so that we chose 1.5 and 5 mg/kg i.v. disopyramide for the present experiments. Disopyramide 1.5 mg/kg i.v. increased the blood pressure soon after injection and decreased the heart rate, but it failed to change the respiratory rate or gross behavior of the

Fig. 1. Effects of intravenous disopyramide on the blood pressure (BP), heart rate (HR) and respiratory rate (RR) of conscious beagle dogs. * $p < 0.05$ and ** $p < 0.01$ against the 0 time values.

animals. With 5 mg/kg i.v. also the blood pressure increased, but, unlike the case where 1.5 mg/kg i.v. was used, the heart rate increased for over 10 min. Blood pressure elevation lasted longer than the chronotropic effect. There were no changes in the respiratory rate throughout the study period.

Procainamide (Fig. 2)

Since 20 mg/kg i.v. procainamide was effective in suppressing digitalis arrhythmia in dogs (Hashimoto et al. 1983) and 60 mg/kg was necessary for suppressing two-stage coronary ligation arrhythmia in dogs in our previous studies (Hashimoto et al. 1982), we examined the effects of 20 and 60 mg/kg i.v. procainamide. With 20 mg/kg the blood pressure slightly increased in the conscious animals, but there were no other changes. Sixty mg/kg i.v. also slightly increased the blood pressure, but produced long lasting tachycardia of more than 30 min duration. Procainamide did not change the respiratory rate, but induced vomiting within 5 min in 6 of 7 dogs.

Lidocaine (Fig. 3)

Lidocaine 2 mg/kg i.v. was effective in suppressing digitalis arrhythmia (Hashimoto et al. 1983), but 10 mg/kg i.v. was required to suppress adrenaline arrhythmia in our previous paper (Shibuya et al. 1983). This 10 mg/kg i.v. lidocaine induced convulsions in conscious coronary ligated dogs without an appreciable antiarrhythmic effect (Hashimoto et al. 1982). On the basis of these previous observations, we chose 2 and 6 mg/kg for the present study. Two mg/

Fig. 2. Effects of intravenous procainamide.

Fig. 3. Effects of intravenous lidocaine.

kg i.v. lidocaine induced only a slight increase in the blood pressure, soon after injection. However, 6mg/kg i.v. induced excitation with spastic extremities and in 4 of 6 dogs tonic convulsions. The blood pressure, heart rate and respiratory rate increased for about 5 min. The higher dose of lidocaine induced vomiting in 1 of 6 dogs.

Phenytoin (Fig. 4)

We used 5 and 10 mg/kg i.v. for three ventricular arrhythmia models (Hashimoto et al. 1982, 1983; Shibuya et al. 1983), and showed that phenytoin was effective in all of them. We chose a smaller dose of 3 mg/kg i.v. and an effective dose of 10 mg/kg i.v. for the present study. Three mg/kg phenytoin transiently increased both the blood pressure and heart rate. Ten mg/kg increased the heart rate dose-dependently, but the increase in the blood pressure, though minimal, was longer lasting. This dose of phenytoin excited conscious dogs, induced vomiting in 2 of 7 dogs and increased the respiratory rate.

Fig. 4. Effects of intravenous phenytoin.

Verapamil (Fig. 5)

Verapamil was effective only on adrenaline arrhythmia at 0.1 mg/kg i.v. (Shibuya et al. 1983), while 0.3 to 1 mg/kg induced severe hypotension without antiarrhythmic effects on digitalis and two-stage coronary ligation arrhythmias (Hashimoto et al. 1982, 1983). We examined 0.1 and 0.3 mg/kg i.v. in the present experiments. Both doses of verapamil induced only slight hypotension soon after injection, but dose-dependent tachycardia. Though there were no marked behavioral changes, the respiratory rate slightly increased after 0.3 mg/kg i.v. There were no cases of sinus arrest or A-V block after i.v. verapamil.

Fig. 5. Effects of intravenous verapamil.

DISCUSSION

The present experiments revealed that in conscious dogs, antiarrhythmic drugs did not exert marked depressive effects on the cardiovascular system, but instead often produced hypertensive and positive chronotropic effects in higher doses as summarized in the right panel of Table 1. Disopyramide and procainamide increased both the blood pressure and the heart rate without changing the respiratory rate. Similar effects of disopyramide on the blood pressure and heart rate were reported by Walsh and Horwitz (1979) using almost similar doses in conscious dogs. The blood pressure in the conscious dog with coronary ligation arrhythmia was also increased by disopyramide, but the blood pressure of dogs with other arrhythmias was not increased. There were no increases in the total heart rate or atrial rate of dogs with arrhythmias as compared with the present results on conscious normal dogs. Disopyramide has been reported to have a negative, and procainamide to have a positive, inotropic effect (Hashimoto et al. 1978, 1979). Also, both drugs are known to have anticholinergic action (Kumana and Hamer 1979; Bigger and Hoffman 1980), and disopyramide has a direct vasoconstrictor effect (Walsh and Horwitz 1979; Toda et al. 1981). Walsh and Horwitz (1979) reported that disopyramide increased the blood pressure of conscious dogs by its direct vasoconstrictor effect and increased the heart rate by its anticholinergic action. It must be emphasized that, though seemingly no deleterious effects occurred after disopyramide, it depressed the inotropic state dose-dependently (Walsh and Horwitz 1979). Though only speculative, procainamide might have increased the blood pressure by its positive inotropic effect and increased the heart rate by its anticholinergic actions.

TABLE 1. *Comparison of the cardiovascular effects of antiarrhythmic drugs on dogs with ventricular arrhythmias and the present conscious dogs*

Drugs	Arrhythmia	Effects on dogs with ventricular arrhythmias					Effects on conscious dogs			
		Dose (mg/kg)	Arrhythmic Ratio	THR	Atrial Rate	BP	Dose (mg/kg)	HR	BP	RR
Disopyramide	Cor	5	Dec	Dec	No	Inc	1.5	Dec	Inc	No
	Adr	3	Dec/Inc	Dec/	Dec	No/	5	Inc	Inc	No
	Dig	3	Dec	Dec	Dec	No				
Procainamide	Cor	60	Dec	Dec	No	No	20	No	Inc	No
	Adr	10-60	Inc	Dec	Dec	No	60	Inc	Inc	No
	Dig	20	Dec	Dec	Dec	No				
Lidocaine	Cor	10	No	No	Inc	Inc	2	No	Inc	No
	Adr	10	Dec	Dec	Dec	No	6	Inc	Inc	Inc
	Dig	2	Dec	Dec	Dec	Dec				
Phenytoin	Cor	10	Dec	Dec	Inc	Dec	3	Inc	Inc	No
	Adr	5	Dec	Dec	No	Dec	10	Inc	Inc	Inc
	Dig	10	Dec	Dec	Dec	Dec				
Varapamil	Cor	0.3	No	Dec	No	Dec	0.1	Inc	No	No
	Adr	0.1	Dec	Dec	Dec	Dec	0.3	Inc	No	Inc
	Dig	1	No	Dec	Dec	Dec				

Cor, two-stage coronary ligation arrhythmia; Adr, halothane-adrenaline arrhythmia; Dig, ouabain arrhythmia; THR, total heart rate; BP, blood pressure; HR, heart rate; RR, respiratory rate; Dec, decrease; Inc, increase; No, no statistically significant effect. Decrease in the arrhythmic ratio indicates antiarrhythmic effects and increase in the arrhythmic ratio, arrhythmogenic effect. The left panel was produced from our previous papers (Hashimoto et al. 1982, 1983; Shibuya et al. 1983).

Procainamide produced emesis, but disopyramide had no such effect. Lidocaine and phenytoin increased the blood pressure, heart rate and respiratory rate simultaneously with excitation. These changes must have been induced by central mechanisms, because, as shown in Table 1, lidocaine and phenytoin had only direct negative effects on the isolated cardiac preparations (Hashimoto et al. 1978, 1979). This transient tachycardia was the antiarrhythmic mechanism of lidocaine on the two-stage coronary ligation arrhythmia by overdriving the ventricular rhythm (Hashimoto et al. 1982). In the case of verapamil, tachycardia occurred as has been already reported in conscious dogs, and this effect has been shown to be produced by the autonomic reflex (Nakaya et al. 1983). No tachycardia was observed in dogs with arrhythmias, and only bradycardia and hypotension were verapamil's effects.

The cardiovascular effects of antiarrhythmic drugs on conscious normal dogs were not all consistent with our previous studies on antiarrhythmic drugs using conscious and anesthetized dogs (Table 1). Our present experiments revealed that bradycardia and hypotension induced by antiarrhythmic drugs which occurred in anesthetized dogs could not be observed in healthy conscious dogs. Though cardiovascular depression must occur after antiarrhythmic drug injection without decrease in the heart rate or blood pressure as in the case of disopyramide (Walsh and Horwitz 1979), the present experiments indicate that these drugs may be administered relatively safely when therapeutic doses were used. In the case of intravenous verapamil, it is usually thought to induce bradycardia and A-V block, but clinically, reflex tachycardia was also reported to occur (Kumana and Hamer 1979) as in the conscious dogs (Nakaya et al. 1983).

The present experiments also revealed, by observation of the behavior and recording the change in the respiratory rate, that lidocaine and phenytoin had central stimulant side effects, which seemed to induce generalized sympathetic activation resulting in increase in the heart rate and blood pressure. Procainamide showed an emetic effect in high doses. None of the drugs among the five antiarrhythmic drugs used induced prominent depressant effects on the central nervous system, so these drugs might be administered in severely sick patients without inducing respiratory arrest or depression.

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