Effect of Various Antiarrhythmic Drugs on the Daunomycin-Induced Arrhythmia in the Hamster[1] (34409)

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Daunomycin (NSC-82,151), an antibiotic, has been found to acutely induce a bidirectional ventricular arrhythmia in the hamster (1). Arrhythmias have also been induced experimentally following ouabain (2), ligation of the anterior descending coronary artery (3), administration of epinephrine during cyclopropane anesthesia (4) or hypothermia (5). Numerous studies have shown that these arrhythmias can be suppressed by various types of drugs including *beta* adrenergic blocking compounds. The present study was initiated to determine to what extent the daunomycin arrhythmias in the hamster are modified by antiarrhythmic drugs.

Methods and Materials. Male golden hamsters weighing between 90 to 140 g were used in all experiments. Anesthesia was induced with an intraperitoneal (ip) injection of 45 mg/kg of sodium pentobarbital (Nembutal). A standard lead II electrocardiogram (ECG) was monitored from needle electrodes inserted into the appropriate limbs and heart rate was determined by means of a cardiotachometer. In some experiments, right carotid artery blood pressure was monitored through a Sanborn 267B transducer and respiratory movements were detected by means of a differential pressure transducer attached to a tracheal cannula. All parameters were recorded with a Hewlett-Packard polygraph.

Each hamster was administered 50 mg/kg of daunomycin. A supplemental dose of 25 mg/kg was then given if the ECG pattern did not become abnormal within 15 min. The challenge agents or saline were given over a 2-min period when the arrhythmia had been established for 5 min. The onset and duration of any antiarrhythmic activity were recorded. Heart rates were determined prior to daunomycin, prior to and following test drug administration. Experiments were terminated 30 min following test drug administration.

Drugs, calculated as the free base, were dissolved in physiological saline prior to the beginning of each experiment. Injections were made through a fermoral vein cannula in a dose volume of 0.1–0.2 ml followed by a 0.2-ml saline wash.

The compounds studied and doses (mg/kg) were: *dl*-propranolol hydrochloride (Inderal) (0.25, 0.5, 1.0, and 2.0), *d*-propranolol hydrochloride (1.0, 2.0, and 4.0), diphenylhydantoin sodium (Dilantin) (12.5 and 25.0), quinidine sulfate, (1.5, 3.0, and 6.0) procainamide hydrochloride (Pronestyl) 1.2, 6.0, and 20.0), lidocaine hydrochloride (Xylocaine) (1.0, 5.0, and 10.0) *dl*-[4-2 (-isopropylamino-1-hydroxyethyl) methanesulfonanilide hydrochloride] (*dl*-MJ 1999) (1, 3, and 6.0) and D(—)-*l*-*N*-isopropyl-*P*-nitrophenyl-ethanolamine hydrochloride D (—)-*l*-INPEA) (10 and 25).

Results. Daunomycin was administered to 112 hamsters. In the majority of these experiments, a 50 mg/kg dose induced a bidirectional ventricular arrhythmia similar to the ECG pattern reported previously (1). The injection of 0.2 ml of physiological saline, in 5 experiments, failed to influence the course of the arrhythmia which continued for an average of 35 min. The antiarrhythmic activity of the other test compounds is summarized in Fig. 1.

Diphenylhydantoin. This agent antagon-

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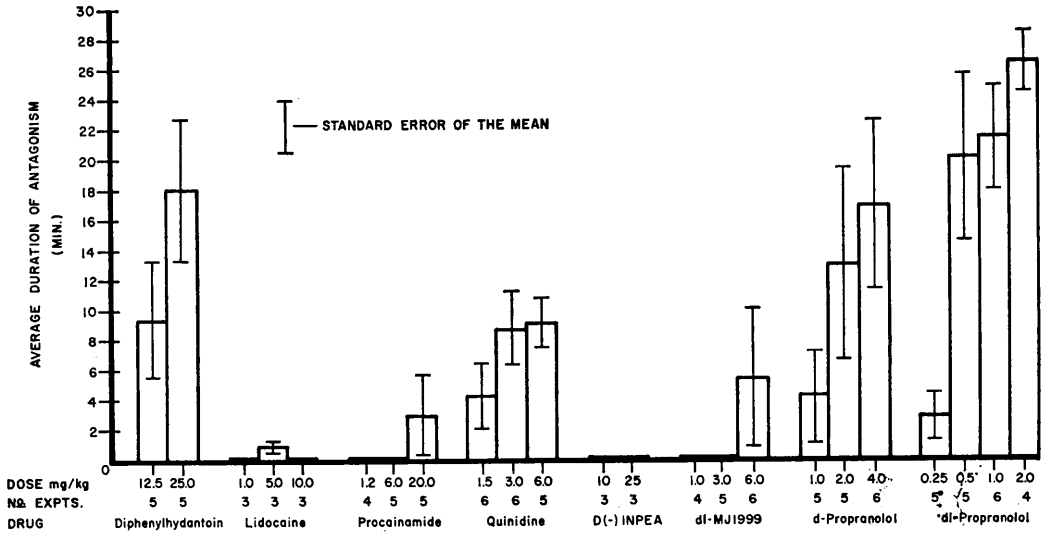

FIG. 1. Average duration of antagonism of various doses of diphenylhydantoin lidocaine, procainamide, quinidine, D(—)-INPEA, *dl*-MJ-1999, *d*-propranolol and *dl*-propranolol against the ventricular arrhythmia-induced by daunomycin in the hamster.

ized the daunomycin arrhythmia for average periods of 9.4 and 18.0 min at 12.5 and 25 mg/kg, respectively. In all cases of antagonism the ECG returned to control within 1.5 min following injection. Diphenylhydantoin had little effect on blood pressure and produced a slight decrease in heart rate at the higher dose.

Lidocaine. Lidocaine exerted little antiarrhythmic activity at any dose but did depress heart rate 17–35%. At 10 mg/kg, additional toxicity was seen in the form of abnormal QRS complexes and in one experiment fatal heart block.

Procainamide. A dose of either 1.2 or 6.0 mg/kg had little effect on blood pressure and heart rate and produced no antiarrhythmic activity. The 20.0 mg/kg dose caused a decrease in both heart rate and blood pressure (28–36 mm Hg) which gradually returned toward control values over a 10–15-min period. In one experiment, procainamide converted the arrhythmia to a sinus rhythm for approximately 15 min while in others bizarre QRS complexes and heart block were observed.

Quinidine. Antiarrhythmic activity was exerted by all doses of quinidine for average periods of from 4.2 to 9.1 min. Although the arrhythmia was eliminated during these periods the resulting ECG patterns were not entirely normal. In some experiments a persistent 2:1 heart block appeared while in others the sinus rhythm had smaller P and T waves or larger QRS complexes than those observed during the control period. In addition, the 3.0 and 6.0 mg/kg doses also produced a long-lasting depression (35–45 mm Hg) in mean arterial blood pressure and a 27–29% decrease in heart rate.

D(—) *INPEA.* Both 10.0 and 25.0 mg/kg doses exerted little antiarrhythmic activity except for a brief 1-min period of sinus rhythm observed in one experiment. In other experiments, particularly at the higher dose, alterations were noted either in the amplitude or the shape of the ventricular complex pattern. This dose also depressed mean arterial blood pressure 20 mm Hg and heart rate 50% over a 10–15-min period.

dl-MJ 1999. MJ 1999 showed antagonism against the daunomycin arrhythmia in 4 of 15 experiments. In only one of these experiments was the reversion to sinus rhythm maintained for over 2.5 min. In some experiments, the 3.0 and 6.0 mg/kg doses altered the size and shape of the complexes but the resulting changes were not entirely normal

and thus the arrhythmia was not considered to be antagonized. The higher doses also consistently caused a transient decrease of 16–20 mm Hg in mean arterial blood pressure and a prolonged 20–29% decrease in heart rate.

d- and dl-Propranolol. Both isomers of propranolol exerted dose related antagonism of the daunomycin arrhythmia. At comparable doses racemic propranolol was found to exert significantly more antiarrhythmic activity than dexpropranolol. In all instances, except for a decreased heart rate, the sinus rhythm induced by these compounds was identical in appearance to the control. Heart rate was decreased 9–20% by dexpropranolol and 17–41% by racemic propranolol. Both isomers also produced a transient dose related 6–30 mm Hg decrease in mean arterial blood pressure.

Discussion. The daunomycin arrhythmia was most effectively antagonized by diphenylhydantoin and propranolol and to a lesser extent by quinidine. In the present experiments diphenylhydantoin caused an immediate reversion to normal sinus rhythm in all experiments. Antiarrhythmic activity persisted for longer periods at the 25 mg/kg dose. This agent has also been found to suppress effectively ouabain and other experimentally induced supraventricular and ventricular arrhythmias (3–6).

Some have suggested that the mechanism of action of diphenylhydantoin might differ from that of quinidine-like drugs (7, 8). This idea is supported by the present experiments where diphenylhydantoin produced a normal sinus rhythm with minimal heart rate depression while the antiarrhythmic activity of quinidine was marked by additional toxicity and depression of heart rate. Although quinidine did significantly modify the daunomycin arrhythmia there were many instances of additional abnormalities even following reversion to sinus rhythm. This toxicity could be due to an interaction of certain cardiac properties of daunomycin with those of quinidine. Such interaction also limits the clinical use of quinidine in digitalis toxicity (9).

Other drugs such as procainamide (10), and lidocaine (11) possess cardiac actions similar in many respects to quinidine. In contrast to quinidine these agents were relatively ineffective against the daunomycin arrhythmia although both procainamide and lidocaine do show some activity against ouabain toxicity (6, 12). Levitt and Roberts (13) suggested that quinidine modifies certain digitalis arrhythmias by diminishing adrenergic nervous activity. Such an action, if operative in the present experiments, might explain the increased effectiveness of quinidine as compared to procainamide and lidocaine against the daunomycin arrhythmia.

The most effective agent tested, racemic propranolol, antagonized the daunomycin arrhythmia at lower doses than dexpropranolol. A similar quantitative antiarrhythmic difference between the isomers of propranolol was observed against ouabain induced toxicity in cats and dogs (13). From these results it appears that the antiarrhythmic activity exerted by dexpropranolol is due to the quinidine-like or local anesthetic properties common to many of the isomers of *beta* adrenergic blocking compounds. On the other hand, our studies with INPEA and MJ 1999 indicate that the daunomycin arrhythmia does not respond to a simple reduction in cardiac sympathetic influence and heart rate. Thus, the present experiments together with those of Barrett and Cullum (14) indicate that the antiarrhythmic activity of a cardiodepressant compound such as *dl*-propranolol is enhanced if simultaneous *beta* adrenergic blockade also occurs.

Summary. The influence of various cardiodepressant and *beta* adrenergic blocking drugs on the daunomycin induced bidirectional arrhythmia in the hamster was determined. Diphenylhydantoin reverted the arrhythmia to sinus rhythm with minimal decreases in heart rate and blood pressure. Quinidine exerted some antiarrhythmic activity but the resulting ECG patterns were not normal in most cases. In addition, the higher doses produced a persistant decrease in heart rate and blood pressure. These results support the evidence that the antiarrhythmic action of diphenylhydantoin is different from quinidine. Other quinidine-like agents such as lidocaine and procainamide exerted minimal

antiarrhythmic activity. The most effective agent tested racemic propranolol antagonized the arrhythmia at lower doses than dexpropranolol although each isomer decreased heart rate. Both D(—)-INPEA and *dl*-MJ 1999 exerted almost no antiarrhythmic activity. These results tend to indicate that antagonism of the daunomycin arrhythmia is due to actions other than *beta* receptor blockade but in the case of racemic propranolol these actions are enhanced if simulataneous *beta* adrenergic receptor blockade also occurs.

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1. Herman, E. H., Schein, P., and Farmar, R. M., Proc. Soc. Exptl. Biol. Med. **130**, 1098 (1969).

2 Zapata-Diaz, J., Cabrera, E. and Mendez, R., Am. Heart J. **43**, 854 (1952).

3. Harris, A. S. and Kokernot, R. H., Am. J. Physiol. **163**, 505 (1950).

4. White, C. W., Jr, Megirian, R., and Swiss, E. D., Circulation Res. **3**, 290 (1955).

5. Covino, B. G., Wright, R., and Charleson, D. A., Am. J. Physiol. **181**, 54 (1955)

6. Mosey, L. and Tyler, M., Circulation **65**, (1954).

7. Bigger, J. T., Jr., Harris, P. D., and Weinberg, D. I., J Cardiol. **19**, 119 (1967).

8. Helfant, R. H., Scherlag, B. J., and Damato, A. N., Circulation **36**, 108 (1967).

9. Moe, G. K. and Abildskov, J. A. *in* "Pharmacological Basis of Therapeutics" (L. S. Goodman and A. Gilman, eds.) p. 707. Macmillan, New York, (1965).

10. Bellet, S. *in* "Cardiovascular Drug Therapy" (A. N. Brest and J. J. Moyer, eds.) p. 477. Grune and Stratton, New York (1965).

11. Sugimoto, T., Schaal, S. F., Dunn, N. M., and Wallace, A. G., J. Pharmacol. Exptl. Therap. **166**, 146 (1969).

12. Morrow, D. H. and Bosomworth, P. P., Anesthesia, Analagesia, Current Res. **46**, 183 (1967).

13. Levitt, B. and Roberts, J., Circulation Res. **19**, 622 (1966).

14. Barrett, A. M. and Cullum, V. A., Brit. J. Pharmacol. **34**, 43 (1968).

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