Effect of Several Anticonvulsant Drugs and Procainamide against Ouabain-Induced Cardiac Arrhythmias in Rabbits

WILLIAM E. DRESSLER, G. VICTOR ROSSI▲, and RAYMOND F. ORZECHOWSKI

Abstract □ Sodium diphenylhydantoin, trimethadione, mephenytoin, ethotoin, methsuximide, and procainamide were compared for their ability to antagonize ouabain-induced cardiac arrhythmias in anesthetized rabbits. Diphenylhydantoin (40 mg./kg. i.v.) prevented the development of arrhythmia in four of six rabbits and significantly prolonged the onset of arrhythmia in the remaining two animals. Pretreatment with either procainamide (25 mg./kg. i.v.) or trimethadione (500 mg./kg. i.v.) significantly delayed arrhythmia onset but failed to block the appearance of ouabain-induced arrhythmias. Mephenytoin, ethotoin, and methsuximide did not exhibit antiarrhythmic activity at nontoxic doses in this test system.

Keyphrases □ Antiarrhythmic activity—evaluation and comparison of diphenylhydantoin, trimethadione, mephenytoin, ethotoin, methsuximide, and procainamide □ Procainamide—antiarrhythmic activity evaluation, comparison with five anticonvulsant drugs □ Anticonvulsant drugs—evaluation as antiarrhythmic agents

The anticonvulsant drug diphenylhydantoin was shown to antagonize several types of experimental cardiac arrhythmias, including those induced by coronary ligation (1), toxic doses of digitalis (2), epinephrine–cyclopropane (3), acetylcholine (4), and aconitine (5). Diphenylhydantoin has been employed successfully in the clinical management of cardiac arrhythmias resulting from digitalis overdosage (6). Other anticonvulsant drugs exhibited varying degrees of antiarrhythmic activity in experimental animals. For example, mephenytoin and trimethadione were found to be effective against cardiac arrhythmias produced by intraventricular injection of picrotoxin, pentylenetetrazol, or deslanoside but not against arrhythmias induced by intravenous administration of deslanoside (7). Mephenytoin and primidone partially protected dogs against atrial fibrillation evoked by acetylcholine (4). Carbamazepine antagonized arrhythmias induced by either digitalis or coronary ligation (8).

Based on these observations of antiarrhythmic activity with various anticonvulsants, and on the continuing need for agents effective against arrhythmias associated with digitalis toxicity, a number of anticonvulsant compounds were evaluated for their ability to inhibit digitoxic arrhythmias. This report is concerned with a comparative study of the protective effect of procainamide, diphenylhydantoin, and other clinically effective anticonvulsant drugs against cardiac arrhythmias induced by ouabain in rabbits.

EXPERIMENTAL

Male New Zealand white rabbits (1.8–2.4 kg.) were anesthetized[1], a tracheotomy was performed, and each animal was heparinized (2 mg./kg. i.v. of sodium heparin). The systemic arterial blood pressure, heart rate, ECG (Lead II or III), and respiration were recorded continuously on a multichannel recorder; the ECG was monitored simultaneously on an oscilloscope.

The test compound or solvent was administered by slow intravenous infusion (femoral vein) during a 5–10-min. period. Five minutes after completion of the pretreatment, a 150-mcg./kg. challenge dose of ouabain was infused intravenously during a 2-min. period. Arrhythmia incidence, time of onset of arrhythmia, and deaths during the 60-min. period after ouabain administration were noted. An arrhythmia was considered to be electrographic evidence of ectopic activity persisting longer than 15 sec. The time of onset was measured from the start of the ouabain infusion to the first appearance of an arrhythmia.

In drug-pretreated rabbits, protection was considered to be complete if an arrhythmia failed to develop during the 60 min. following infusion of ouabain. Protection was considered to be partial in those instances where an arrhythmia occurred but in which the onset was delayed more than 2 standard deviations from the control group mean value. The Wilcoxon Rank-Sum Test (9) was employed in a comparison of the mean times of arrhythmia onset between drug-treated and solvent-control groups.

The following drugs and doses were evaluated for their ability to prevent ouabain-induced arrhythmias in anesthetized rabbits: sodium diphenylhydantoin[2] (20 and 40 mg./kg.), mephenytoin[3] (20 mg./kg.), ethotoin[3] (80 and 160 mg./kg.), trimethadione[4] (500 mg./kg.), methsuximide[2] (80 mg./kg.), and procainamide hydrochloride[5] (25 mg./kg.). Ouabain[6] was dissolved in a 0.9% NaCl solution; diphenylhydantoin was solubilized in water by the addition of one drop of 1 *N* NaOH. Trimethadione was administered in aqueous solution, while mephenytoin, ethotoin, and methsuximide were dissolved in 60 or 95% ethanol so that the total amount administered did not exceed 0.5 ml./kg. of 95% ethyl alcohol. The proprietary procainamide hydrochloride injection was used.

RESULTS AND DISCUSSION

Preliminary experiments established that intravenous injection of 150 mcg./kg. of ouabain consistently evoked cardiac arrhythmias in rabbits. This finding is in agreement with results reported by Peterson and Ciofalo (10). The characteristic arrhythmic response to ouabain included frequent extrasystoles of A-V junctional and ventricular origin. In approximately 50% of the solvent-treated control animals, ventricular tachycardia and fatal ventricular fibrillation also occurred within 60 min. of ouabain administration.

The effects of five anticonvulsant drugs and procainamide against ouabain-induced arrhythmias in rabbits are summarized in Table I.

In this study, frequent complete protection was observed only in the group pretreated with 40 mg./kg. of diphenylhydantoin. In four of six experiments at this dose level, ouabain-induced arrhythmias were completely blocked; in the remaining two experiments, the onset of arrhythmia was prolonged significantly. Pretreatment with 20 mg./kg. of diphenylhydantoin appeared to increase the time of arrhythmia onset in some animals, but there was no statistically significant difference between treated and control mean values. All animals pretreated with either 20 or 40 mg./kg. of diphenylhydantoin survived the ouabain challenge compared to 50% mortality among controls; however, statistical validation of the improved survival incidence was not possible because of the small sample sizes.

[1] With Dial-Urethane (0.6 ml./kg. i.v.), Ciba Pharmaceutical Co.

[2] Parke, Davis & Co.
[3] Sandoz Pharmaceuticals.
[4] Abbott Laboratories.
[5] E. R. Squibb & Sons.
[6] Calbiochem.

Table I—Effects of Several Anticonvulsant Drugs and Procainamide against Ouabain-Induced Cardiac Arrhythmias in Rabbits

Treatment	Arrhythmia Incidence[a]	Arrhythmia Onset (min.), Mean ± *SD*	Protection			Percent Animals Protected, Complete or Partial	60-min. Survival Incidence[a]
			Complete[b]	Partial[c]	None		
Vehicle control (diphenylhydantoin solvent), 0.8 ml./kg.	6/6	2.42 ± 0.66	—	—	6	0	3/6
Sodium diphenylhydantoin:							
20 mg./kg.	5/6	4.02 ± 2.98	1	2	3	50	6/6
40 mg./kg.	2/6	10.5[d]	4	2	0	100	6/6
Procainamide hydrochloride, 25 mg./kg.	5/6	6.38 ± 0.99[d]	1	5	0	100	5/6
Trimethadione, 500 mg./kg.	6/6	4.00 ± 1.08[d]	0	4	2	67	2/6
Vehicle control (95% ethanol), 0.5 ml./kg.	7/7	2.91 ± 0.85	—	—	7	0	3/7
Mephenytoin, 20 mg./kg.	6/6	2.62 ± 0.83	0	0	6	0	2/6
Ethotoin:							
80 mg./kg.	6/6	2.05 ± 0.54	0	0	6	0	1/6
160 mg./kg.	2/5[e]	4.0	0	1	1	50	1/2
Methsuximide, 80 mg./kg.	6/6	2.47 ± 1.19	0	0	6	0	1/6

[a] All ratios are expressed as number observed/number tested. [b] No arrhythmia during 60-min. observation period. [c] Arrhythmia occurred, but onset exceeded control group mean by more than 2 standard deviations (*SD*). [d] Significantly different from control value ($p < 0.05$), Rank-Sum test. [e] Three rabbits died during ethotoin infusion (not included in "survival incidence" column).

Procainamide at a dose level of 25 mg./kg. was less effective in this test system than was 40 mg./kg. of diphenylhydantoin inasmuch as complete protection was obtained in only one of six procainamide-pretreated rabbits; partial protection was observed in the remaining five animals. The mean time of arrhythmia onset in procainamide-pretreated rabbits was significantly greater than that of the vehicle control group. Procainamide, like diphenylhydantoin, was reported to be effective in converting ouabain-induced ventricular tachycardia to normal sinus rhythm in dogs (11).

Trimethadione, 500 mg./kg., significantly prolonged the mean onset of arrhythmia. Of the six rabbits tested, four were partially protected according to the parameters defined; however, only two animals survived the 60-min. observation period. During the intravenous infusion of trimethadione, several rabbits developed transient apnea which required mechanically assisted respiration.

Mephenytoin, ethotoin, and methsuximide neither prevented ouabain-induced arrhythmias nor improved survival at the maximal doses that could be infused without producing severe hypotensive shock. Although partial protection was observed in one of two rabbits successfully pretreated with ethotoin, 160 mg./kg., three other animals died during infusion of this dose before ouabain could be administered. Adamska-Dyniewska *et al.* (12) reported that mephenytoin and trimethadione failed to suppress ouabain-induced cardiac ectopic activity in cats. Clinically, mephenytoin was used successfully in a limited number of patients exhibiting atrial and ventricular arrhythmias (13).

In summary, diphenylhydantoin was superior to several other anticonvulsant drugs and procainamide in preventing cardiac arrhythmias resulting from ouabain infusion in anesthetized rabbits. Mephenytoin, ethotoin, and methsuximide failed to exhibit antiarrhythmic activity in nontoxic doses in this test system. Trimethadione appeared to prolong arrhythmia onset but did not improve survival incidence.

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▲ To whom inquiries should be directed.