Antiarrhythmic Properties of Dimebon

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The H_1-receptor blocker Dimebon is shown to exhibit pronounced antiarrhythmic properties. Its activity and therapeutic action range (toxic/therapeutic ratio) exceed those of quinidine, ethmosine, isoptin, and bonnecor in several animal models of cardiac arrhythmia. The mechanism of its antiarrhythmic action is probably associated with blockade of sodium and particularly calcium channels, prolongation of the effective refractory period, and slowing of impulse traffic in the conduction system of the heart. Dimebon may be recommended for submission to clinical trials as an antiarrhythmic agent.

Key Words: *Dimebon; antihistamines; antiarrhythmics*

Dimebon [3,6-dimethyl-9-(2-methyl-pyridyl-5)-ethyl-1,2,3,4-tetrahydro-γ-carboline dihydrochloride] is a new Russian-made antihistamine blocking H_1 receptors [5]. The present study was undertaken to test Dimebon for antiarrhythmic activity in view of the evidence that the myocardium contains H_1 receptors and that certain antihistamines are capable of suppressing arrhythmias in experimental animals [4,10].

MATERIALS AND METHODS

The study used 205 male Wistar rats (body weight 0.18-0.22 kg); 48 random-bred rabbits (2.3-3.4 kg), 56 cats (2.6-3.2 kg) and 35 dogs (12-18 kg) of both sexes, as well as 16 and 36 preparations of isolated frog and guinea pig atria (trabeculae and auriculae), respectively.

The acute toxicity (median lethal doses, LD_{50}) of Dimebon and other antiarrhythmic drugs tested for comparison was measured in rats.

The effects of the drugs on electrocardiographic parameters (*R*, *RR*, *QT*, *PQ*, *QRS*) were evaluated on Nembutal-anesthetized cats (40 mg/kg intraperitoneally); electrocardiograms were recorded in the standard lead II at 3, 5, 10, 15, and 20 min and then every 10 min for 60 min postadministration. Dawes' method as modified by Alles and Ellis [11] was used to measure the effect of the drugs on the highest reproducible contraction frequency of isolated guinea pig atria. The drugs were compared for antiarrhythmic activity (AAA) by determining the concentration that prolonged the effective refractory period (ERP) by 15% (EC_{15}). The effects of Dimebon (10^{-5} M) on action potentials and transmembrane ionic currents were tested on trabeculae of frog (*Rana ridibunda*) atria [12].

The ability of the drugs to exert antiarrhythmic activity in mixed atrial/ventricular arrhythmias was assessed using models of arrhythmias induced by aconitine [3], epinephrine [9], and calcium chloride [14] in rats, barium chloride [6] in rabbits, and strophanthin [1] in cats. The end-points used in these experiments were the median effective dose (ED_{50}), which eliminated arrhythmia in 50% of the test animals, and the LD_{50}/ED_{50} ratio, which gives an indication of the therapeutic (antiarrhythmic) action range of the drug used. In addition, Dimebon and two other drugs were also tested for effects on atrial [15] and ventricular [13] arrhythmias in dogs. The activity of the drugs in atrial arrhythmia was measured by the method of bio-

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TABLE 1. Comparative Antiarrhythmic Activities and Therapeutic Action Ranges of Dimebon, Isoptin, Bonnecor, and Quinidine in Animal Models of Arrhythmia Induced by Epinephrine (Rats), Strophanthin (Cats), Calcium Chloride (Rats), and Barium Chloride (Rabbits)

Drug	ED_{50} (mg/kg) in arrhythmia induced by				LD_{50} of 0.5% solution, mg/kg	LD_{50}/ED_{50}			
	A	S	CCh	BCh		E	S	CCh	BCh
Dimebon	0.1 (41.0)	2.8 (5.1)	10.8 (1.04)	1.4 (6.1)	58.6 (0.9)	586.0	20.9	5.4	41.9
Isoptin	1.2 (3.4)	0.5 (28.8)	1.0 (11.2)	0.7 (12.1)	15.3 (3.5)	12.8	30.6	15.3	21.9
Bonnecor	1.4 (2.9)	No effect	1.6 (7.0)	0.5 (17.0)	11.9 (4.6)	8.5	–	7.4	23.8
Quinidine	4.1 (1)	14.4 (1)	11.2 (1)	8.5 (1)	54.2 (1)	13.2	3.8	4.8	6.4

Note. E = epinephrine, S = strophanthin, CCh = calcium chloride, BCh = barium chloride. Figures in parentheses are the values relative to that of quinidine taken as unity.

logical titration [16] and their activity in ventricular arrhythmia, by counting the number of ectopic contractions and expressing it in percent relative to the frequency of cardiac contractions per min recorded by the electrocardiograph 24 h after the descending branch of the left coronary artery was occluded.

Quinidine, isoptin, ethmosine, and bonnecor were used as reference drugs. All drugs, including Dimebon, were mainly administered in increasing doses, by the intravenous route in *in vivo* tests. The results were subjected to statistical analysis [2,8].

RESULTS

Dimebon at 2.5 mg/kg did not cause significant changes in electrocardiographic parameters. At 5 mg/kg it significantly increased the intervals *RR* (by 16% and 20% after 10 and 30 min, respectively), *PQ* (by 6% after 5, 10, and 30 min and 12% after 60 min), and *QT* (by 23% after 10, 30, and 60 min); widened the *QRS* complex (by 13% after 10 min and 16% after 30 min); and tended to depress the *R* wave (between minutes 5 and 20).

Dimebon proved to be far superior to the other three drugs in terms of the ability to prolong the ERP. Thus, its EC_{15} (2.5×10^{-8} M) was higher by factors of 172, 14, and 21, respectively, than that of quinidine (4.3×10^{-6} M), ethmosine (3.5×10^{-7} M), and bonnecor (5.2×10^{-7} M).

In the tests with isolated atrial trabeculae, Dimebon caused a significant (35%) increase in the threshold for current in 3-6 min, accompanied by 26% and 9% decreases in the duration of the action potential at the plateau level and at the base, respectively, with little or no change in the amplitude of this potential. The rapid inward sodium current decreased by 18%, while the reversal potential for the sodium current, at which the latter became equal to zero, increased from 90 to 105 mV. The slow inward calcium current decreased by 23%, with virtually no change in the reversal potential. The instantaneous outward potassium flux increased by 44% in the potential region of 40-100 mV.

Dimebon in doses of 2.5, 5, and 10 mg/kg failed to display AAA in the animal model of aconitine-induced arrhythmia, but did manifest marked AAA in the arrhythmias caused by epinephrine, strophanthin, calcium chloride, or barium chloride (Table 1). In the epinephrine-in-

TABLE 2. Effects of Dimebon (5 mg/kg), Ethmosine (5 mg/kg), and Isoptin (0.25 mg/kg) on Ventricular Arrhythmia in Dogs ($M\pm m$; $n=5$)

Time, min	Heart rate (beats/min)			% of ectopic contractions/min		
	Dimebon	ethmosine	isoptin	Dimebon	ethmosine	isoptin
Baseline	171.0±6.00	163.0±3.86	164.8±4.72	78.0±4.93	76.0±6.00	73.4±5.00
1	182.0±5.79	144.0±7.08*	173.2±4.51	74.0±5.36	4.0±0.64***	67.8±6.44
3	187.0±5.36	129.0±6.00**	176.2±5.58	35.0±3.86***	9.0±1.29***	52.2±8.60
5	183.0±6.87	119.0±6.45**	171.8±6.01	5.0±1.07***	14.0±1.98***	41.4±6.65**
10	167.0±6.86	118.0±4.93***	165.6±5.15	3.0±0.64***	22.0±1.72***	3.0±0.86***
15	159.0±5.36	124.0±5.79***	163.0±4.51	8.0±1.29***	55.0±8.15	2.4±0.64***
20	156.0±8.70	137.0±6.45**	161.0±5.36	62.0±4.93	68.0±7.08	8.2±1.50***
30	163.0±7.08	142.0±7.51*	162.6±5.79	79.0±4.51	84.0±2.36	51.4±6.87*
40	167.0±5.36	148.0±6.45	162.2±6.01	86.0±2.79	82.0±4.93	72.8±3.65

Note. *$p<0.05$, **$p<0.01$, ***$p<0.001$ relative to baseline.

duced model of arrhythmia, its AAA and therapeutic range (as estimated by calculating the LD_{50}/ED_{50} ratio) exceeded 41-fold and 44-fold, respectively, those of quinidine, 14-fold and 69-fold those of bonnecor, and 12-fold and 46-fold those of isoptin. In the strophanthin-induced model of arrhythmia, Dimebon was 5 and 6 times more efficacious than quinidine, but 6 and 1.5 times less so than isoptin in terms of AAA and therapeutic range, respectively. Bonnecor did not exhibit significant AAA at 0.5, 1, or 2 mg/kg in the strophanthin-induced arrhythmia and even aggravated the latter in a higher dose (3 mg/kg).

Dimebon was less active in the calcium chloride-induced model of arrhythmia; in this model, its AAA and therapeutic range were comparable to those of quinidine but inferior to those of bonnecor (7- and 1.4-fold, respectively) and isoptin (11- and 3-fold). Finally, in the barium chloride-induced arrhythmia, the AAA of Dimebon was 6 times higher than that of quinidine but 3 and 2 times lower, respectively, than those of bonnecor and isoptin, while its therapeutic range was 6.5, 1.7, and 1.8 times wider, respectively, than those of quinidine, bonnecor, and isoptin.

Dimebon also manifested pronounced AAA in atrial arrhythmia. The dose eliminating atrial fibrillation (3.1±0.15 mg/kg) was much lower than that of quinidine (23±1.25 mg/kg; $p<0.001$) or ethmosine (9.2±1.67 mg/kg; $p<0.01$). Incremental isoptin doses (0.8-1.2 mg/kg) led to a progressive slowing of the heart rate and to extrasystoles, creating a threat of cardiac arrest, and for this reason no further "biological titration" of this drug was attempted.

In ventricular arrhythmia (Table 2), Dimebon at 5 mg/kg significantly reduced the number of ectopic contractions between minutes 3 and 15 postinjection, this effect peaking at minute 10. The antiarrhythmic effect of ethmosine in the same dose (5 mg/kg) was at its height during the 1st minute postinjection and persisted for 10 min. Isoptin at 0.25 mg/kg began exerting an antiarrhythmic effect by the 5th minute and caused the greatest decrease in the number of ectopic contractions by the 15th minute; its AAA persisted for 27 min on average. Dimebon and isoptin showed only a tendency to increase the heart rate in the first 1 to 5 min postinjection; after ethmosine administration, in contrast, the heart rate remained significantly increased from the 1st to the 30th minute.

Dimebon is thus capable of acting as an antiarrhythmic agent and, as found using several animal models of cardiac arrhythmia, is superior to certain established antiarrhythmic drugs in terms of AAA and the therapeutic action range (i.e., the toxic/therapeutic ratio). The antiarrhythmic effects of Dimebon can probably be attributed to its membrane-stabilizing action with respect to sodium and especially calcium ion channels and its ability to prolong the myocardial ERP and to slow impulse traffic in the supraventricular and ventricular parts of the cardiac conduction system. It is therefore recommended that this compound undergo clinical trials with a view to its use as an antiarrhythmic according to new indications.

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