SOME ASPECTS OF THE ACTION OF KNOWN ANTIARRHYTHMIC AGENTS

V. M. Samvelyan and M. V. L'vov

UDC 615.22.015.4:616-008.924.1

KEY WORDS: calcium chloride arrhythmia; lidocaine; metabolic projection of the myocardium.

According to modern views on the pathogenetic role of disturbance of calcium homeostasis in the development of ischemic heart disease, the mechanism of the antianginal action of Ca^{++} ion antagonists consists essentially in reducing the mechanical work of the heart and the oxygen consumption and improving the blood supply to the cardiac muscle. However, clinical observations show that metabolic protection of the myocardium due to inhibition of the system for entry of Ca^{++} ions into the cells can be effected not only by specific calcium antagonists, such as verapamil and nifedipine, but also by other drugs. In particular, to limit the zone of ischemia and myocardial infarction certain antiarrhythmic agents are widely used, especially lidocaine, for which clinicians have awarded preference evidently not only because of its antifibrillation properties [9, 10].

To study intra- and extracardial relations between the anticalcium action of certain antiarrhythmic agents. their activity was compared on models of calcium chloride arrhythmia, on explants of the embryonic myocardium and on anesthetized rats.

EXPERIMENTAL METHOD

Cellular arrhythmia was produced in explants of myocardium from 6-8-day chick embryos incubated in medium containing 80% Eagle's medium and 20% horse serum [5]. Distinct disturbances of the rhythm of contractions appeared after the addition of $CaCl_2$ to the chambers containing explants in a concentration of 1×10^{-5} g/ml and in a volume of 0.1 ml. Contractions were recorded by means of the photoelectric effect on a specially built apparatus. Molar concentrations of Ca^{++} ions which prevented and abolished cellular arrhythmia were determined. Experimental arrhythmia was produced in albino rats anesthetized with urethane and chloralose by intravenous injection of $CaCl_2$ in doses of 200 to 250 mg/kg. Rhythm disturbances were recorded by means of a two-channel ELKAR-2 electrocardiograph. Known antiarrhythmic drugs with different methods of action were studied: inderal (propranolol), ethmozine,* quinidine, procainamide, lidocaine, and also the specific Ca^{++} ion antagonists verapamil, nifedipine, and segontin.† Each dose was studied on five animals and eight explants. The drugs were injected into the femoral vein.

EXPERIMENTAL RESULTS

Addition of $CaCl_2$ to the chambers with contracting explants caused disturbance of the rhythmic contractions after 1 min, with alternation of slowing and quickening. After 2 min the rhythm of contractions quickened, and one or several regular phases of contraction were omitted, so that typical arrhythmia developed, and after 23 ± 2 min it led to irreversible arrest of spontaneous activity (Fig. 1a). All the drugs studied except procainamide had both a prophylactic and a therapeutic action to varied degree on the cellular model of arrhythmia. In all the experiments, in order to abolish the arrhythmia concentrations one order of magnitude below the preceding concentrations were added. The most marked antiarrhythmic properties were found in the case of the specific Ca^{++} ion antagonist verapamil, which abolished established arrhythmia in a concentration of 2.2×10^{-10} M. The antiarrhythmic activity of nifedipine

*2-carbethoxyamino-10-(3-morpholylpropionyl)-phenothiazine HCl.
†Prenylamine.

Laboratory of Pharmacology and Pathophysiology, Institute of Cardiology, Ministry of Health of the Armenian SSR, Erevan. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 95, No. 6, pp. 72-75, June, 1983. Original article submitted December 17, 1982.

0007-4888/83/9506-0807$07.50

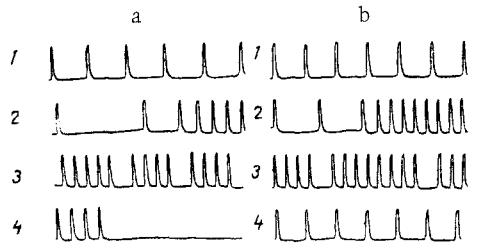

Fig. 1. Photoelectrogram of contractions of explants of chick embryonic myocardium. a) Arrhythmogenic action of $CaCl_2$: 1) normal rhythm of contractions, 2) addition of $CaCl_2$ in a concentration of 1×10^{-5} g/ml, 3) 1 min later, 4) 2 min later – complete arrest of spontaneous activity; b) antiarrhythmic action of lidocaine: 1) normal rhythm of contractions, 2) addition of $CaCl_2$, 3) addition of lidocaine in a concentration of 3×10^{-8} M, 4) complete abolition of arrhythmia.

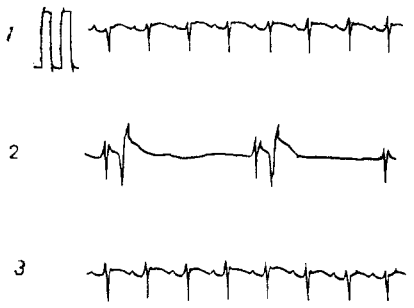

Fig. 2. Effect of lidocaine on $CaCl_2$-induced arrhythmia in albino rats. 1) Original ECG in standard lead II, 2) intravenous injection of $CaCl_2$ in a dose of 250 mg/kg, 3) injection of lidocaine in a dose of 0.3 mg/kg completely restores the sinus rhythm.

(1.4×10^{-8} M) was somewhat weaker. Lidocaine also had a similar and considerable antiarrhythmic action (Fig. 1b), and the same was true also of inderal and ethmozine. Segontin, however, a specific but weaker Ca^{++} antagonist than verapamil and nifedipine, and also quinidine abolished $CaCl_2$-induced arrhythmia in higher concentrations. Procainamide had practically no such activity. All the drugs studied appreciably slowed the frequency of rhythmic contractions of the explants after abolishing the arrhythmia. This slowing amounted on average to 14%, and only quinidine caused not only bradycardia (to 30-35%), but also a marked decrease in amplitude of the contractions.

Comparison of the antiarrhythmic properties on a model of $CaCl_2$-induced arrhythmia in animals revealed a somewhat different pattern of relationships between their activity although the general trend of their action remained the same as before. The most active drug on this model was lidocaine which, in a dose as little as 0.3 mg/kg had a complete and prolonged antiarrhythmic action. None of the other antiarrhythmic drugs tested had so strong an antagonism against $CaCl_2$, even such powerful and specific Ca^{++} antagonists as verapamil and nifedipine. The β-adrenoblocker inderal had a somewhat weaker action in the experiments on animals and its activity was less than that of ethmozine, segontin, and quinidine. Data on the antiarrhythmic action of lidocaine in experiments on albino rats are given in Fig. 2. The relative activity of the various substances on the two models of $CaCl_2$-induced arrhythmia are shown graphically in Fig. 3.

The pathogenetic role of disturbances of electrolyte homeostasis in the onset and abolition of arrhythmias is not in dispute. Disturbances of the electrophysiological parameters of heart muscle connected with changes in conductance for Na^+, K^+, and, more recently, for Ca^{++} have been the subject of much research [6, 13]. Considerable similarly in the mechanisms of action of many antiarrhythmic drugs and local anesthetics have been demonstrated. Definite

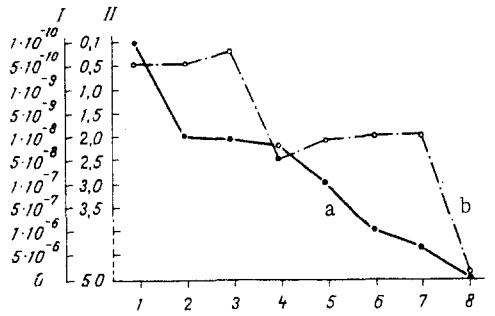

Fig. 3. Relationship between intra- and extracardial antiarrhythmic action of various drugs. Abscissa, drugs studied: 1) verapamil, 2) nifedipine, 3) lidocaine, 4) inderal, 5) ethmozine, 6) segontin, 7) quinidine, 8) procainamide; ordinate: I) concentration (in M), II) dose (in mg/kg). a) Explants of embryonic myocardium, b) animals.

correlation exists between these properties [3, 14]. Many antiarrhythmic drugs have been found to cause identical changes in electrophysiological parameters, but in experiments on animals and, still less, in clinical practice, they are by no means equally active.

It has been shown that procainamide, quinidine, ethmozine, and lidocaine block conduction of Na^+ ions to a considerable degree, thereby causing hyperpolarization and stabilizing the resting membrane potential, causing slowing of conduction of impulses. Quinidine, lidocaine, and lidoflazine also affect the K^+ ion gradient, normalizing the intra- and extracellular K^+ ion levels and they accelerate repolarization processes, leading to the abolition of arrhythmias [6, 13]. Antiarrhythmic drugs of the verapamil type act on the calcium component of the action potential, shortening it. They are effective in arrhythmias arising by a mechanism of recurrent excitation.

In recent years an important role in generation of the action potential of damaged myocardial cells and pacemaker cells, with an initially low transmembrane potential difference, has been ascribed to the slow inward Ca^{++} current. However, as examination of many published investigations shows, very complex relations exist between the calcium and potassium currents, and this makes it difficult to predict the antiarrhythmic effects of drugs blocking transmembrane Na^+ (quinidine, inderal, procainamide, etc.) or Ca^{++} transport [12]. Many drugs with no direct effect on calcium conduction of the membrane may thus have an indirect action on it through their effect on penetration of Na^+ and K^+ ions. Consequently, the same drug may serve more than one intracardial mechanism of action. On the whole animal, its extracardial effect may also be manifested.

Recent data are evidence of the important role of lipids and proteins in the action of local anesthetics and of antiarrhythmic drugs on conductance of excitable membranes. Their action at times changes to the diametrically opposite depending on the concentration used [2, 12]. It has been shown in the case of procainamide that it interacts with the membrane, modifies the conformation of globular protein, and replaces it by calcium. The presence of hydrophobic interactions between molecules of local anesthetic and phospholipids is confirmed by data on the ability of local anesthetics to displace Ca^{++} ions adsorbed on molecular films of acid phospholipid [7, 8]. It has been shown in the case of antiarrhythmic drugs of the phthalazine series that one way in which they block conduction channels is by replacing Ca^{++} ions at corresponding sites of the membrane by other agents [1, 4]. Another method of blocking may perhaps be through conformational changes in the structure of the globular proteins of the membrane. This change evidently reduces the effectiveness of Ca^{++} ions in the regulation of membrane permeability. The two processes are interconnected. The authors cited conclude from their results that to ensure an effective antiarrhythmic action of drugs their ability to displace Ca^{++} ions from protein structures must also be taken into account. There are indications [11] that membranes of different types of cells respond to elevation of the intracellular Ca^{++} level by an increase in permeability for K^+ ions. The β-adrenoblockers are indirectly able to reduce the entry of Ca^{++} [9, 10]. The Ca channels in the myocardium are controlled by changes in the cell membrane potential, however brought about — whether intracardially (usually) or extracardially (more rarely). Blockade of the Na channel by

tetrodotoxin (selectively), or by local anesthetics or antiarrhythmic drugs (less selectively) must therefore have some effect on the state of the Ca channels.

Our own experiments provide proof of the considerable extracardial influence of lidocaine maintaining and potentiating its intracardial anticalcium action. This is evidently the reason for the great superiority of lidocaine over other antiarrhythmic drugs in the treatment of myocardial infarction, for the end result of its marked anticalcium action, equal to that of verapamil and nifedipine, endow it with considerable antihistamine properties as well as its antiarrhythmic properties.

LITERATURE CITED

1. Kh. L. Gainutdinov, E. V. Narusevicius, et al., in: Biophysics of Membranes [in Russian], Part 2, Kaunas (1972), pp. 173-178.
2. A. E. Grinfel'd and E. V. Narusevicius, in: Biophysics of Membranes [in Russian], Part 2, Kaunas (1972), pp. 196-202.
3. Zh. A. Dyadyura and M. V. L'vov, Farmakol. Toksikol., No. 2, 170 (1975).
4. E. L. Ivchenko and E. V. Narusevicius, in: Biophysics of Membranes [in Russian], Part 1, Kaunas (1971), pp. 395-409.
5. M. N. L'vov, "The search for new antiarrhythmic drugs and some mechanisms of their action," Author's Abstract of Candidate's Dissertation, Erevan (1972).
6. E. Carmeliet, Verch. Kon. Acad. Geneesk. Belg., 37, 229 (1976).
7. J. Cerbon, Biochim. Biophys. Acta, 290, 51 (1972).
8. H. Hauser and R. M. Dawson, Biochem. J., 109, 909 (1968).
9. W. G. Neiler, in: Ninth World Congress of Cardiology, Abstracts, Vol. 1, Moscow (1982), No. 0072.
10. L. H. Opie, in: Ninth World Congress of Cardiology. Abstracts, Vol. 1, Moscow (1982). No. 0070.
11. W. Putney, in: Calcium in Drug Action, New York (1978), pp. 173-194.
12. H. A. Tritthert, in: Calcium-Antagonismus, Berlin (1980), pp. 42-54.
13. A. I. Undrovinas, A. V. Yushmanova, and L. V. Rosenshtraukh, J. Mol. Cell. Cardiol., 12, 171 (1980).
14. V. V. Zakusov, N. T. Pryanishnicova, and V. M. Samvelyan (V. M. Samvelian), Croat. Chem. Acta, 52, 171 (1979).