ON THE ANTIARRHYTHMIC ACTIVITY OF ISOTEOLINE (IST)

M. Markov, D. Zhelyazkov, G. Yakimov

Key-words: isoteoline – arrhythmia – glaucine – therapy

The use of various experimental models of arrhythmias varying in pathogenetical details from each other enables the relatively adequate evaluation of substances which are potential candidates for medicinal drugs designated for treatment of cardiac arrhythmias. The former experimental practice (10) has proved the reliability of this approach in looking for and creating of new means preventing or correcting cardiac rhythmic disorders. Based on literature data about the pathogenesis of single kinds of experimental arrhythmias they can be conditionally divided into two main groups: 1. Arrhythmias in the genesis of which a cardinal role is played by receptor and probably pre-receptor adrenergic mechanisms. Adrenalin, strophantin and barium arrhythmias belong to this category. 2. Arrhythmias resulting from disturbed post-receptor intracellular mechanisms. Both calcium and aconitine arrhythmias can be ranked to a great extent in this group (3). This classification of models of arrhythmias used by us is close to V. Williams' one (11) and provides a good basis for understanding the mechanisms of antiarrhythmic means.

The purpose of the present work is to study by using some experimental models of arrhythmias selected from these two groups mentioned the antiarrhythmic activity of isoteoline (IST) obtained by a previously described method (1) and to compare it with that of glaucine, being its derivative.

Material and Methods

Experiments were carried out on 32 white male rats of Wistar breed with mean body weight of 253 ± 14 g narcotized with thiopental-sodium at dosis of 40 mg/kg i.p.; 8 non-narcotized rabbits with mean body weight of 2600 ± 0.600 g, and 6 guinea-pigs narcoitzed with uretane at dosis of 1.2 g/kg i.p. (mean body weight of 620 ± 70 g). Rhythmic disorders were registered on 12-channel polyphysiograph "Galileo" or on monochannel electro-cardiograph "Cardiomet". The following models of arrhythmia were used: induced by adrenalin in rats (after I. Gilbert et al., 1959); induced by barium dichloride in non-narcoitzed rabbits (after L. Szekeres and P. Papp, 1971); by strophantin K in guinea-pigs (after H. Schmitt et Mme H. Schmitt, 1960); by calcium dichloride in rats (after M. Malinov et al., 1955), and by aconitine in rats (after M. Fekete and I. Dorsy, 1964).

Results and Discussion

The negative chronotropic effect of IST (2) that is previously reported presents a principle precondition for a possible antiarrhythmic activity. This was our initial reason to study the potential antiarrhythmic activity of IST in these 5 models of arrhythmia mentioned different not only concerning the inducing agent but also concerning the mechanisms of their development.

The adrenalin arrhythmia in rats induced by i.v. administration of 60 mkg/kg adrenalin is characterized by rapid transitoriness, polytopic ventricular extrasystoles, and sinus bradycardia. IST injection precedes adrenalin one by 2 min with protection purpose. IST exerts a manifested

and long-lasting (more than 60 min) protective effect concerning this kind of arrhythmia at doses of 0.5, 1.0 and 5.0 mg/kg i.v. (fig. 1).

The barium arrhythmia in non-narcotized rabbits is induced by injection of 2% barium dichloride solution at doses of 2 and 4 mg/kg in the auricular marginal vein. Rhythmic disorders

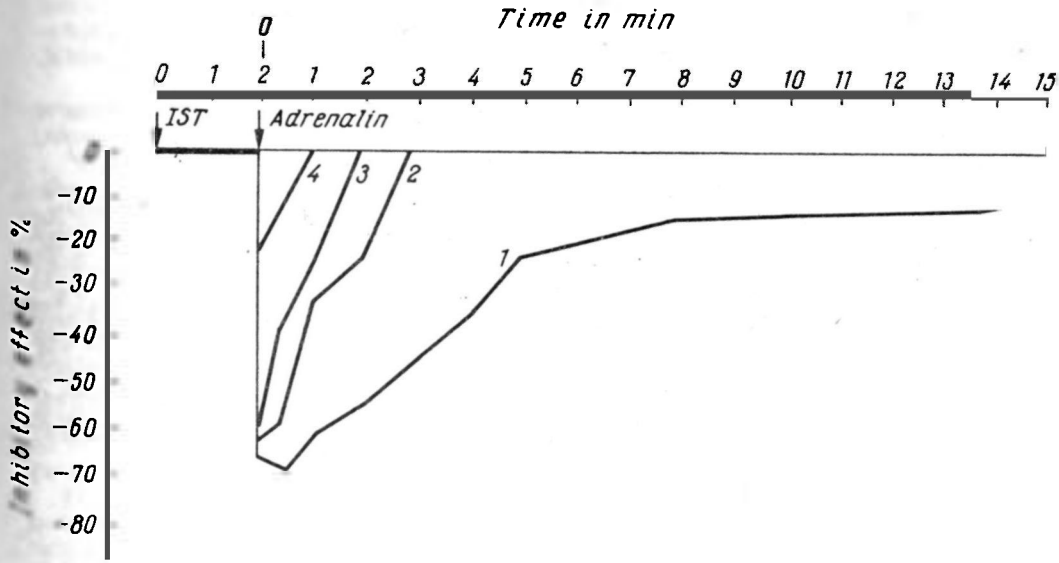

Fig. 1. Dependence of IST protective effect on its dosis in adrenalin arrhythmia in rats. Heart rate changes caused by adrenalin prior to (1) and after IST administration are followed-up.
1 – Adrenalin 60 μg/kg i.v.; 2 – Adrenalin after 0.5 mg/kg i.v. IST; 3 – Adrenalin after 1 mg/kg i.v. IST; 4 – Adrenalin after 5 mg/kg i.v. IST

followed-up for 30 min occur usually on the 15th-30th sec after injection of arrhythmogenic agent and are characterized by polymorphous ventricular extrasystoles, bigeminy-type, sinus bradycardia and AV-block manifestations. Both IST and glaucine are applied at doses of 0.5 and 2.0 mg/kg i.v. 5 min prior to (in a prophylactic regimen) and on the 2nd min after barium dichloride injection (in a therapeutic one). The results obtained show that IST at these doses exerts an expressed antiarrhythmic effect concerning barium arrhythmia in rabbits, both protectively and therapeutically applied. However, glaucine does not possess any antiarrhythmic activity with this model of arrhythmia.

Strophantin arrhythmia induced in guinea pigs by i.v. injection of 200 mkg/kg strophantin K is characterized by delayed AV conduction, ventricular tachycardia and extrasystoles. Protectively, IST was applied at dosis of 0.5 mg/kg 5 min prior to, or on the 1st min after strophantin induction with therapeutic purpose. It is found out that IST has a good protective effect on arrhythmia but no therapeutic one.

Calcium arrhythmia in rats is induced by i.v. injection of calcium dichloride as 10% solution at dosis of 120 mg/kg. Still on the 15th sec after introduction of the agent a severe arrhythmia sets in manifested with polytopic ectopic foci and ventricular fibrillation resulting in lethal outcome for 2–4 min. IST is used with protective purpose only, i.e. 5 min prior to calcium dichloride injection, at doses of 5 and 10 mg/kg i.v. It is established that IST does not demonstrate any antiarrhythmic activity.

Aconitine arrhythmia in rats is induced by slow i.v. injection of aconitine at dosis of 60 mg/

kg. To this purpose aconitine solution in concentration of 0.2% is ex tempore prepared by adding of 2 drops 0.1 nHCl to distilled water and then stored at dark and cool conditions because of its light sensitivity. Usually, on the 30th sec after aconitine application severe disorders of cardiac rhythm can be observed characterized by polytopic ventricular extrasystoles passing into paroxysmal tachycardia, atrial fibrillation and flickering, and lethal outcome (heart arrest in diastole) in 100 per cent of the cases on 10th – 15th min. IST can not influence upon rhythmic disturbances when it is applied at doses of 5 and 10 mg/kg i.v. neither in a prophylactical, nor in a therapeutical regimen.

These results show that IST applied at relatively low doses (0.5 – 2.0 mg/kg) manfiests its antiarrhythmic activity in cases of adrenalin, barium and strophantin arrhythmias. However, it can not influence calcium and aconitine arrhythmias even at doses of 5.0 – 10.0 mg/kg i.v.

These data are of interest mainly because they reveal that IST is a substance acting not only prophylactically but also therapeutically in cases of rhythmic disturbances of heart activity with stress genesis. Second, they indicate that it will be useful in prophylaxis of arrhythmias induced by cardiac glycosides. In this respect its activity is analogous to that of other well-known central D_1-dopaminergic agonists such as bromocryptin, apomorphin, piribecyl, etc., which realize their protective effect by means of activation of central dopaminergic mechanisms at area postrema level resulting in reduction of peripheral sympathetic activity (4). At last, the data showing that IST is ineffective in aconitine and calcium arrhythmias where, as mentioned, sympathetic mechanisms are not pathogenetically involved, also point that IST realizes most effects of its rich pharmacology principally by means of central reduction of peripheral sympathetic activity.

REFERENCES

1. Желязков, Д., Н. Мол лов, М. Марков, С. Филипов, Н. Георгиев, М. Савова, М. Маркова, А. Малеева, Н. Търколев. Авт. свидет. № 34200, ИНРА, 1983. – 2. Желязков, Д., М. Марков, Н. Георгиев, М. Тасков. *Експерим. мед. и морфол.*, 1965, № 1, 13–19. – 3. C a i l l a r d, C., J. L u i s. *Meth. Find. Experim. Clin. Pharmacol.*, 2, 1980, No 5, 225–252. – 4. F a l k, R., R. D e s i l v a, B. L o w n. *Cardiovasc. Res.*, 15, 1981, No 5, 175–180. – 5. F e k e t e, N., J. D o r s y. *Med. Experim. (Basel)*, 10, 1964, No 2, 93–102. – 6. G i l b e r t, J., G. L a n g o, C. B r o c k s. *Circul. Res.*, 7, 1959, 417. – 7. N e l k o, C., R. N. G i l l i c, *J. Pharmacol. Experim. Ther.*, 207, 1978, No 2, 265–270. – 8. M a l i n o v, M., F. B a t l e, D. M a l a m u d. *Arch. Internat. Pharmacodyn. Ther.*, 102, 1955, 266. – 9. S c h m i t t, H., M m e H. S c h m i t t. *Arch. Internat. Pharmacodyn. Ther.*, 127, 1960, 163–179. – 10. S z e k e r e, L., J. P a p p. In: Experimental cardiac arrhythmias and antiarrhythmic drugs. Budapest, Akademia Kiado, 1971, 448. – 11. W i l l i a m s, V. In: Symp. on cardiac arrhythmias. Denmark, 1970, 449–501.

К ВОПРОСУ ОБ АНТИАРИТМИЧЕСКОЙ АКТИВНОСТИ ИЗОТЕОЛИНА (ИЗТ)

М.Марков, Д. Желязков, Г. Якимов

РЕЗЮМЕ

Исследована антиаритмическая активность изотеолина при нескольких экспериментальных моделях сердечной аритмии: адреналиновая сердечная аритмия на крысах, бариевая на ненаркотизированных кроликах, строфантиновая на морских свинках и аконитовая и кальциевая на крысах. Нарушения ритма сердца регистрировались при помощи 12-канального полифизиографа „Галлилео" или при помощи одноканального электрокардиографа „Кардиомат".

Полученные результаты показывают, что изотеолин проявляет антиаритмическую активность по отношению к адреналиновой, бариевой и строфантиновой типов аритмии. В то же время не отмечается существенного влияния изотеолина на аконитовую и кальциевую аритмии.

Авторы считают, что антиаритмическая активность изотеолина, установленная при указанных выше моделях экспериментальных моделях сердечной аритмии, связана, по всей вероятности, с понижением симпатической периферической активности, которая реализуется центрально.