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Effect of β-adrenoceptor blocking agents on poststimulatory atrial flutter in the dog, with observations on the participation of adrenergic mechanisms in this experimental arrhythmia

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Summary

1. Four β-adrenoceptor antagonists, *viz.* (±) propranolol (0·5 mg/kg), (−) alprenolol (0·25 mg/kg), practolol (5 mg/kg) and USVC 6524 (20 μg/kg), were tested for their effects on atrial flutter produced by electrical stimulation of the right atrium around the crushed inter-venae-caval bridge in anaesthetized dogs.

2. All the drugs reduced atrial and ventricular rates ; this was followed by the abrupt termination of flutter and restoration to normal sinus rhythm.

3. Since all the drugs (including practolol, which is devoid of local anaesthetic activity) were given in doses just sufficient to block β-adrenoceptors, it indicated that β-adrenoceptor blockade was responsible for their antiarrhythmic property in this test procedure.

4. Further evidences in support of participation of the sympathetic nervous system in poststimulatory flutter were: (i) flutter could not be produced in nine out of ten dogs whose catecholamine stores were depleted by pretreatment with reserpine ; (ii) infusion of adrenaline in these animals resulted in the production of flutter ; (iii) duration of flutter after termination of exposure to adrenaline was a few minutes, which is similar to the brief time previously reported to be taken for the disappearance of catecholamines from the hearts of reserpinized animals.

5. The clinical significance of the above findings is discussed.

Introduction

In order to prevent or reverse serious haemodynamic derangements after atrial flutter in certain situations, immediate restoration of normal sinus rhythm is highly desirable (Friedberg, 1966). This can be satisfactorily achieved by direct current (d.c.) counter-shock. However, there are situations in which d.c. shock is contraindicated and dangerous (Dreifus, 1970) or the facilities for it may not be available and then drugs must be relied upon for the control of flutter. Traditionally, digitalis and quinidine, either alone or in combination, are used for this purpose, but treatment with these drugs may often fail. This warrants the search for an alternative pharmacological approach to flutter. Hence the present work was undertaken to study the effect of some β-adrenoceptor blocking agents in experi-

mental atrial flutter, which was produced according to the method of Rosenblueth & Garcia Ramos (1947). This experimental model was selected since it resembles clinical atrial flutter (Sharma, 1963; Rytand, 1966; Hayden, Hurley & Rytand, 1967).

Since in our preliminary experiments, propranolol (0·5 mg/kg), which is just sufficient to block cardiac β-adrenoceptors in the dog (Lucchesi, Whitsitt & Stickney, 1967), consistently terminated atrial flutter and since participation of adrenergic mechanisms in acetylcholine-induced atrial fibrillation has recently been stressed (Hashimoto, Chiba, Tanaka, Hirata & Suzuki, 1968), further experiments were designed to elucidate the role of the sympathetic nervous system in experimental flutter.

Methods

Poststimulatory atrial flutter

Thirty mongrel dogs (10–18 kg) were anaesthetized by chloralose (80–100 mg/kg, i.v.) and pentobarbitone sodium (6–10 mg/kg). Under positive pressure artificial ventilation, parts of the sternum and ribs directly over the heart were removed. The pericardium was incised and its flaps were sutured over the chest walls to cradle the heart. The right femoral vein was cannulated for intravenous injections. Direct atrial electrograms from the right atrial appendage and conventional bipolar lead II were recorded simultaneously on a two-channel Galileo electrocardiogram.

As described by Rosenblueth & Garcia Ramos (1947), a narrow band of atrial tissue between the superior and inferior vena cava was crushed by a haemostat and the atrium was stimulated electrically for 5–10 s with square waves (duration 1 ms, frequency 20 Hz and 10–20 V). This resulted in the production of atrial flutter in twenty-seven out of thirty animals. For studying the effect of drugs on poststimulatory atrial flutter, the animals were divided into five groups of five or six animals. The first group served as control and was given a single intravenous injection of 5–8 ml of isotonic saline and changes in the rate of atrial flutter were observed for 2 hours. The remaining four groups received a single intravenous injection of the following four drugs in doses which are just sufficient to produce cardiac β-adrenoceptor blockade in the dog: (±) propranolol (0·5 mg/kg) (Lucchesi *et al.*, 1967), (−) alprenolol (0·25 mg/kg) (Åblad, Brogård & Ek, 1967), practolol (5 mg/kg) (Dunlop & Shanks, 1968) and USVC 6524 (0·02 mg/kg) (Levy & Wasserman, 1970). After injection of the drug, the electrocardiogram was continuously recorded until the reversion of flutter to normal sinus rhythm occurred.

Reserpinized animals

Ten mongrel dogs (9–18 kg) received an intramuscular injection of reserpine (0·5 mg/kg) for 2 successive days before the experiment (Bhargava, Kohli, Sinha & Tayal, 1969). These animals required one-third to one-half of the anaesthetic doses of chloralose and pentobarbitone. As described above, the atrium around the crushed inter-venae-caval bridge was stimulated electrically. Nine animals, in which flutter could not be produced, were given intravenous infusions of adrenaline ((0·2–0·4 μg/kg)/min) for 5–10 min, either alone or preceded by tolazoline (10 mg/kg, i.v.). The atrium was again stimulated electrically during adrenaline infusion and the duration of flutter was noted after the termination of exposure to adrenaline.

Drugs

The following drugs were used: (±) propranolol hydrochloride (I.C.I.); (−) alprenolol bitartrate monohydrate (H 56/28, A.B. Hässle); practolol hydrochloride (I.C.I. 50172), USVC 6524, 1-isopropylamino-3-(4-indanoxy)-2-propanol, as hydrochloride (U.S. Vitamin Corp.); adrenaline (Ward, Blenkinsop & Co.); tolazoline hydrochloride (Ciba); reserpine (E. Merck). All the drugs were dissolved in isotonic saline except reserpine which was dissolved in propylene glycol and citric acid. Solutions were prepared on the day of the experiment. Doses are expressed in terms of salts unless otherwise stated.

Results

Effects of drugs on poststimulatory atrial flutter

In the control group (five animals), which received isotonic saline, the rate of flutter varied by less than 5% during the observation period of 2 hours. This indicated the stability and long-lasting nature of this arrhythmia (Sharma, 1963). The average rate of atrial beats in this group and in the drug treated groups (before the injection of drugs) was 517/min (range=434 to 672). The ventricular rate/min ranged from 182 to 336 (average=261) and was usually half that of atria, indicating the presence of approximately 2:1 atrioventricular block. In three animals, however, 3:1 atrioventricular block was observed.

In the remaining groups (twenty-two animals), drugs in β-adrenoceptor blocking doses were injected after the atrial flutter had continued for 35 min, since spontaneous reversion of an arrhythmia of this duration is rare (Arora & Madan, 1956). The effects were similar in all the experiments. At first, both atrial and ventricular rates were decreased. After 0·5–6 min, there was abrupt termination of flutter and establishment of normal sinus rhythm. Immediately before the restoration of sinus rhythm, the atrial and ventricular rates were reduced by 19% and 27% respectively with propranolol, by 15% and 18% respectively with alprenolol, by 18% and 20% respectively with practolol and by 14% and 15% respectively with USVC 6524. The results are summarized in Table 1 and a representative experiment with each drug is shown in Fig. 1.

Atrial flutter in reserpinized animals

Only in one out of ten reserpinized animals was atrial flutter produced after electrical stimulation of the intact area of the right atrium surrounding the crushed inter-venae-caval bridge. This lasted for 25 minutes. In three of the remaining dogs, in which flutter was not produced, electrical stimulation after adrenaline infusion resulted in the appearance of flutter. As was to be expected, adrenaline caused a rise of blood pressure. In order to eliminate the previously reported (Moe, Malton, Rennick & Freyburger, 1948) arrhythmogenic role of rise of blood pressure, tolazoline (10 mg/kg) was given intravenously 10 min before adrenaline infusion in six experiments. Although adrenaline no longer caused an elevation of blood pressure, flutter was again initiated when the electrical stimulus was applied. Whether tolazoline was given or not, the duration of flutter after stopping the adrenaline infusion was always brief and spontaneous reversion to normal sinus rhythm occurred in 3–5 min (mean ± S.E. = 4 ± 0·33).

TABLE 1. *Effects of various β-adrenoceptor blocking agents on experimental atrial flutter in dogs*

Group	Drug	Dose (mg/kg)	No. of dogs	Control H.R./min Mean±S.E.	H.R./min during flutter Mean±S.E.		H.R./min just before R Mean±S.E.		Time* in min Mean±S.E.	H.R./min just after R Mean±S.E.
					Atrial	Ventricular	Atrial	Ventricular		
1	Isotonic saline	5 ml	5	195± 6	513±20	260±13	—	—	—	—
2	(±) Propranolol	0·5	6	209±14	502±18	271±16	404±22	198±13	3·1±0·5	135±13
3	(−) Alprenolol	0·25	6	156± 7	541±30	251±15	462±30	206±13	4·4±0·5	147± 7
4	Practolol	5·0	5	175± 9	511±32	256±18	416±18	205± 6	3·2±0·8	132± 3
5	USVC-6524	0·02	5	200± 5	513±22	268± 9	442±44	228±23	3·1±0·4	154± 6

H.R., Heart rate. R, Reversion to normal sinus rhythm. * Time taken for reversion to normal sinus rhythm after injection of the drug.

Discussion

In poststimulatory atrial flutter, the initial effect of propranolol, alprenolol, practolol and USVC 6524 was to reduce the atrial rate. This was followed by abrupt termination of flutter and the establishment of normal sinus rhythm. It has been previously reported that various drugs effective in poststimulatory atrial flutter usually enhance the ventricular rate at the same time that atrial rate is declining (Brown, 1951 ; Winbury & Hemmer, 1955 ; Arora & Madan, 1956 ; Singh & Sharma, 1961 ; Madan & Pendse, 1963 ; Moe & Abildskov, 1970). The explanation for this was that at slow atrial rates, stronger atrial impulses were transmitted more frequently to the ventricles and that antiarrhythmic drugs facilitated atrioventricular conduction as a result of their vagal blocking action. In the present study ventricular rate was not increased in any experiment but was invariably decreased. This is in agreement with the commonly observed ventricular slowing in patients with atrial flutter treated with β-adrenoceptor antagonists (Gibson & Sowton, 1969). The mechanism for this is the ability of β-adrenoceptor antagonists to induce effective atrioventricular blockade resulting from prolongation of the re-

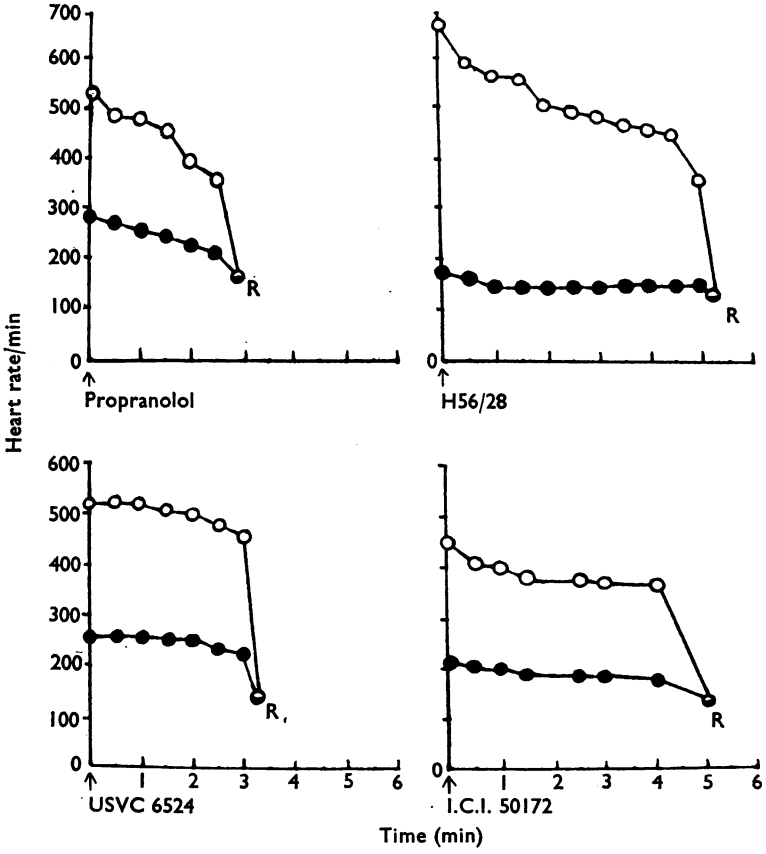

FIG. 1. Effect of propranolol (0·5 mg/kg), L-H 56/28 (alprenolol) (0·25 mg/kg), USVC 6524 (20 μg/kg) and I.C.I. 50172 (practolol) (5 mg/kg) on poststimulatory atrial flutter. Ordinate: number of atrial and ventricular beats/minute. Abscissa: time in minutes. The drugs were given as single intravenous injection at the arrows. Each graph represents results from a different experiment. ○——○, Atrial rate ; ●——●, ventricular rate.

fractory period of the atrioventricular-conducting system, which is largely under the control of adrenergic nervous system (Rouse, 1966).

Numerous investigators have shown that cardiac arrhythmias, in which the role of the sympathetic nervous system is disputed or denied, are not suppressed by all the β-adrenoceptor blocking agents (see Mendez & Kabela, 1970 for references). In such arrhythmias, only those agents which produce quinidine-like or local anaesthetic (membrane-stabilization) actions in doses much higher than those required to block β-adrenoceptors are effective. On the basis of these observations, the relevance of cardiac β-adrenoceptor blockade in mediating the antiarrhythmic effect has been questioned. On the other hand, cardiac rhythm disturbances induced by catecholamines or sympathetic nerve stimulation or by the combination of a sensitizing agent with adrenaline (that is, all arrhythmias in which the involvement of the sympathetic nervous system is clear) are prevented or reversed by all the known cardiac β-adrenoceptor antagonists in doses much lower than those required to produce quinidine-like or local anaesthetic effects (Lucchesi & Whitsitt, 1969). This suggests that their antagonism to catecholamine-induced arrhythmias is mediated by the specific blockade of cardiac β-adrenoceptors. Gibson, Balcon & Sowton (1968) have even suggested that practolol, which exhibits little (Papp & Vaughan Williams, 1969) or no (Dunlop & Shanks, 1968) local anaesthetic activity, can be used in the differential diagnosis of cardiac arrhythmias, since it may be expected to antagonize those caused by sympathetic overactivity but not those which are nonadrenergic in origin.

When the above findings are considered together with the present observations that practolol shares with propranolol, alprenolol and USVC 6524 the property to terminate poststimulatory atrial flutter in doses blocking β-adrenoceptors, the involvement of the adrenergic system in this experimental arrhythmia is implied. In support of this is the observation that in dogs, whose catecholamine stores are depleted by pretreatment with reserpine, atrial flutter could not be produced. Further, in these reserpinized animals, when infusion of adrenaline was given, atrial flutter could be readily induced. However, after termination of exposure to adrenaline, restoration to normal sinus rhythm occurred in 3–5 minutes. The brief duration of atrial flutter in these experiments can be explained by the observations of previous workers that the retention of exogenously administered catecholamines by the tissues of reserpinized animals was only brief. In the experiments of Kopin, Hertting & Gordon (1962), less than 3% of the infused noradrenaline remained in the hearts of reserpinized rats 5 min after termination of the noradrenaline infusion. Similar findings were obtained by Axelrod, Gordon, Hertting, Kopin & Potter (1962). Thus the brief duration of atrial flutter observed in reserpinized, adrenaline treated animals in the present study agrees with the previously reported time taken for the disappearance of catecholamines from the hearts of reserpinized animals. This is interpreted to mean that catecholamines are not only essential for the initiation but also for the maintenance of poststimulatory atrial flutter. Further, it is suggested that the antiarrhythmic effect of propranolol, alprenolol, practolol and USVC 6524 seen in this study is mediated through cardiac β-adrenoceptor blockade.

Clinical significance

β-Adrenoceptor blocking agents have been tried clinically in atrial flutter. Although a decrease in ventricular rate has been consistently observed, the incidence of conversion to normal sinus rhythm has varied from nil (Irons, Ginn & Orgain,

1967; McLean, Stoughton & Kagey, 1967) to 87% (Watt, Livingstone, Mackay & Obineche, 1970). This wide variation in conversion rates may be due to different doses and methods of administration or the concurrent use of other drugs, commonly digitalis (Harrison, Griffin & Fiene, 1965; Gianelly, Griffin & Harrison, 1967). Further, there is enormous biological variation in the doses required to achieve β-adrenoceptor blockade in different individuals (Hill, 1966). Considering the foregoing comments together with the efficacy of propranolol, alprenolol, practolol and USVC 6524 in terminating experimental atrial flutter, which resembles in certain essential features the arrhythmia seen in man (Rytand, 1966; Hayden *et al.*, 1967; Sharma, 1963), further controlled clinical trials of these drugs are warranted. Among them, practolol may be particularly useful because it is a cardioselective β-adrenoceptor antagonist (Dunlop & Shanks, 1968), is less hazardous than propranolol (Dollery, Paterson & Conolly, 1969) and has been found effective even in the presence of cardiac failure (Gibson, *et al.*, 1968).

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