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Effects of (±)-propranolol, (±)-, (+)-, and (−)-alprenolol on unanaesthetized dogs with ventricular arrhythmias resulting from coronary artery ligation

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Summary

1. The effects of (±)-propranolol, (±)-, (+)- and (−)-alprenolol were studied in unanaesthetized dogs with ventricular arrhythmias produced by ligation of the left coronary artery. The responses were compared with those of similar control dogs which were given only isotonic saline.

2. The ventricular arrhythmias were abolished by cumulative doses of 3·5 mg/kg of (±)-alprenolol, 7·5 mg/kg of (−)-alprenolol and (±)-propranolol and by 15·5 mg/kg of (+)-alprenolol.

3. At the time of maximum antiarrhythmic activity none of the drugs produced significant alterations in mean arterial pressure or atrial rate.

4. Cumulative doses of 7·5 mg/kg and 15·5 mg/kg of the four drugs resulted in some instances of lip licking, emesis and/or head tremors while 31·5 mg/kg was invariably lethal.

5. Since the β-adrenoceptor blocking activity of (−)-alprenolol is 100 times greater than that of (+)-alprenolol, suppression of these ventricular arrhythmias was apparently unrelated to antagonism of sympathetic influences.

6. Alprenolol and propranolol have myocardial depressant properties apart from their effects on β-adrenoceptors which could account for the anti-arrhythmic activity observed.

Introduction

The effectiveness of β-adrenoceptor blocking drugs against certain experimental and clinical arrhythmias has been well established (Epstein & Braunwald, 1966). Alprenolol 1-(o-allylphenoxy)-3-isopropylamino-2-propanolol hydrochloride is a new β-adrenoceptor antagonist which is structurally related to both isoprenaline and propranolol (Fig. 1) and which has a blocking potency approximately equal to that of propranolol (Åblad, Brogård & Ek, 1967a; Forsberg & Johnsson, 1967; Johnsson, 1967; Johnsson, Norrby & Sölvell, 1967). Alprenolol has been shown to abolish ouabain-induced ventricular tachycardia in the dog (Duce, Garberg & Johansson, 1967; Proctor & Wasserman, 1967), hydrocarbon-anaesthetic arrhythmias in the cat (Lord, Katz & Eakins, 1968) and various arrhythmias in man (Anthony, Jick & Spodick, 1969: Linko, Siitonen & Ruosteenoja, 1967).

The first objective of the present study was to compare the effects of (±)-alprenolol and (±)-propranolol in the dog with arrhythmias resulting from ligation of the left coronary artery. This preparation was selected because the arrhythmias have been described as aetiologically similar to those which accompany acute myocardial infarction in man (Clark & Cummings, 1956). Second, the relationship between the antiarrhythmic and antiadrenergic actions of (±)-alprenolol was investigated by comparing the effects of its (−)- and (+)-forms which have twice and one-fiftieth the β-adrenoceptor blocking potency of the racemic form respectively (Åblad *et al.*, 1967a, 1967b ; Johnsson, 1967).

Methods

Coronary artery ligation

Fifteen adult mongrel dogs of either sex weighing between 10 and 14 kg were anaesthetized with pentobarbitone sodium, 30 mg/kg intravenously. The heart was exposed through a left thoracotomy and the anterior descending branch of the left coronary artery was ligated in two stages (Harris, 1950). A recording electrode was sutured to the pericardium over the left atrium and its lead exteriorized at the back of the neck to facilitate monitoring of atrial activity. Polyethylene catheters were implanted in the abdominal aorta and the inferior vena cava through the femoral vessels for monitoring pressure (1 mmHg≡1·333 mbar) and injecting test substances respectively.

Conduct of experiments

Experiments were performed without anaesthesia or sedation on the second day after coronary occlusion. Each experiment was conducted with the dog supported in a standing position. Electrocardiograms (atrial and lead II) and the arterial pressure obtained through a Statham P-23AA transducer were recorded on an

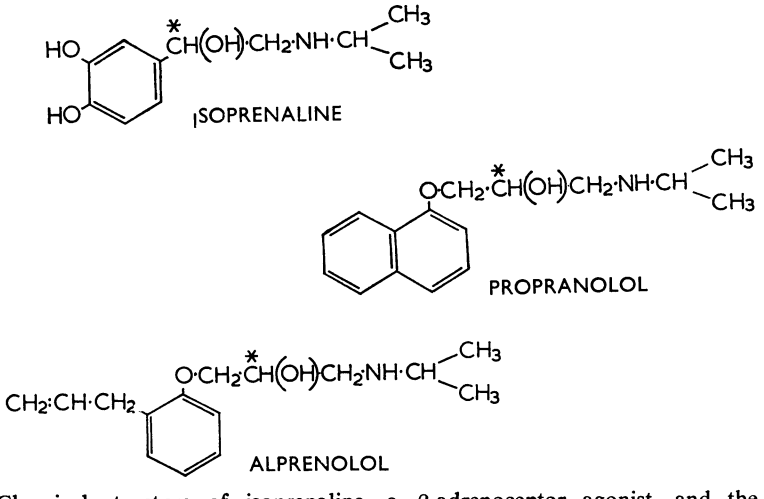

FIG. 1. Chemical structure of isoprenaline, a β-adrenoceptor agonist, and the chemical structures of propranolol and alprenolol, β-adrenoceptor blocking agents. Asymmetric carbon atoms are indicated by an asterisk.

Offner Type R Dynograph. The experiments were divided into five groups of three dogs each. Serial doses of 0·5, 1·0, 2·0, 4·0, and 8·0 mg/kg of (±)-propranolol, (±)-, (−)-, or (+)-alprenolol or repeated doses of 5 ml of isotonic saline were administered intravenously at 30, 30, 30, and 60 min intervals respectively. In some cases a 16·0 mg/kg dose (or 5 ml of saline) was given after an additional hour. All injections were made over a period of 5 min. Records were taken before and at the end of each injection and 5, 10, 20, and 30 min thereafter.

Evaluation of data

The severity of the ventricular arrhythmia was estimated in each record by analysing 100 consecutive beats and classifying those of subatrial origin as ectopic and expressing them as a percentage of the total beats. The lowest incidence of ventricular ectopic beats observed within 30 min of each injection was considered to be the maximum effect of treatment. The criterion for abolition of the arrhythmia was a suppression of the ectopic frequency to less than 5%. In addition, the atrial and total ventricular rates were counted over 20 s and expressed in beats/min.

The data from the first five doses were analysed for statistical significance using either non-parametric procedures described by Siegel (1966) or parametric methods described by Lindquist (1953). Differences were considered significant when $P<0·05$.

Drugs

The hydrochloride salts of (±)-propranolol, (±)-alprenolol and (+)-alprenolol were used whereas (−)-alprenolol was in the tartrate form. The (−)-alprenolol preparation contained less than 0·2% of the *dextro* isomer and (+)-alprenolol contained less than 1·0% of the *laevo* form (Brändström, 1969, personal communication). Solutions were prepared on the day of the experiment. All doses were calculated on the basis of the hydrochloride salt.

Results

Effects of coronary artery ligation

On the second day following ligation of the coronary artery, all fifteen dogs had a ventricular arrhythmia with 70 to 100% of the ventricular complexes being of non-atrial origin. The total ventricular rate (range=127–187 beats/min) was usually higher than the atrial rate (range=88–181 beats/min). The mean arterial pressure ranged from 70 to 125 mmHg. There was no significant difference in these parameters among the five groups of dogs studied (Siegel, 1966).

One group of dogs was given only 5 ml of isotonic saline intravenously at the prescribed intervals. The results obtained in a typical experiment are included in Fig. 2. In general, the lowest incidence of ventricular ectopic beats observed during the first 30 min after each injection average 3–26% less than the control values, reflecting a fluctuation in the severity of these arrhythmias (Table 1). During the periods of lowest ectopic activity the total ventricular rate, atrial rate, and mean arterial pressure were essentially unchanged.

Drug effects

Effect on ventricular ectopic beats

The remaining four groups of dogs were given either (±)-propranolol, (±)-, (−)-, or (+)-alprenolol intravenously. Representative experiments with (±)-propranolol, (±)-, and (+)-alprenolol are depicted in Fig. 2, and the data are summarized in part in Table 1. Ventricular ectopic activity was significantly diminished but not completely suppressed by cumulative doses of 0·5 and 1·5 mg/kg of (±)-alprenolol. It was not significantly altered by the corresponding doses of the

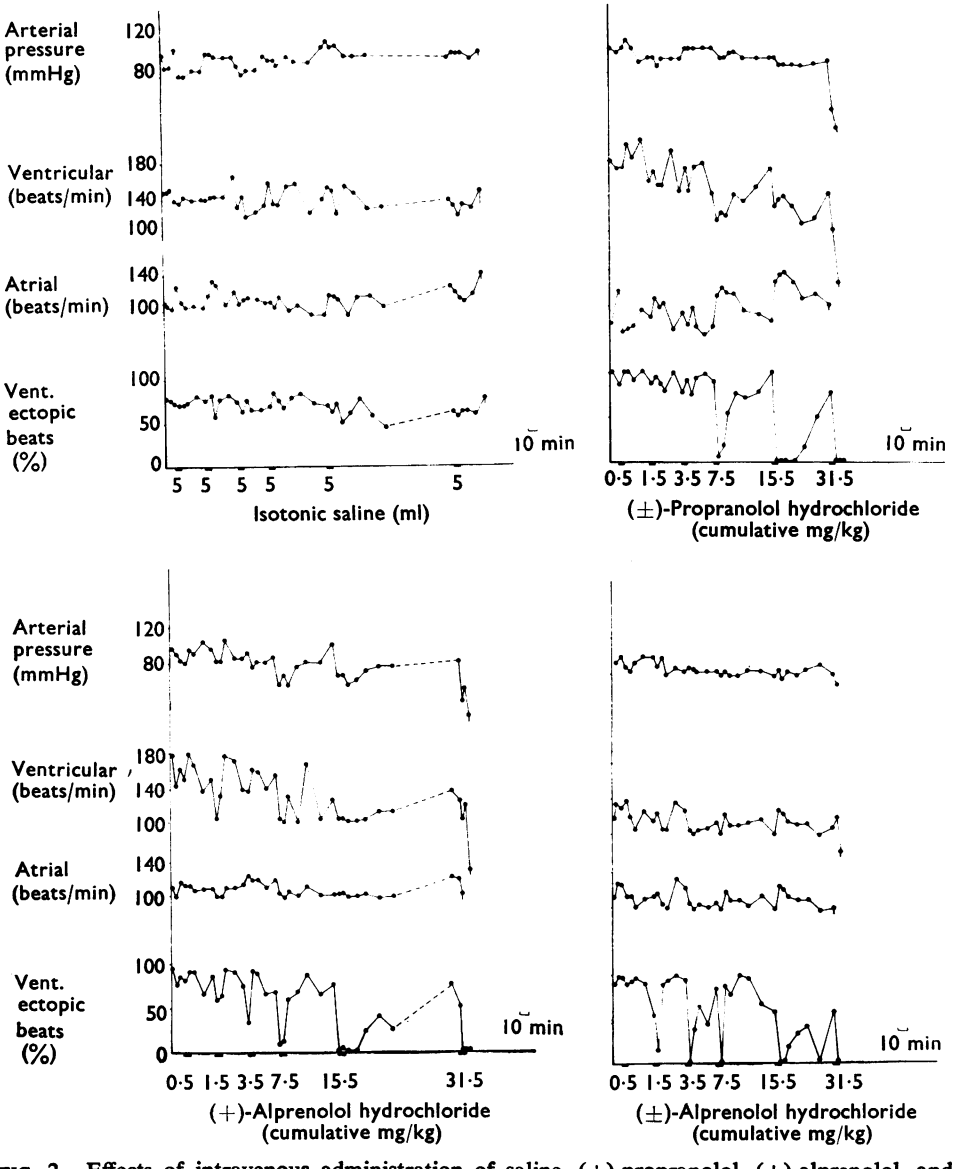

FIG. 2. Effects of intravenous administration of saline, (±)-propranolol, (±)-alprenolol, and (+)-alprenolol on the unanaesthetized dog 2 days after ligation of the coronary artery. Each graph represents a typical experiment.

TABLE 1. *Effect of intravenous administration of saline, (±)-propranolol, (±)-alprenolol, (−)-alprenolol, and (+)-alprenolol on the unanaesthetized dog following coronary artery ligation. Values are means ± S.E. for each compound in three dogs unless otherwise indicated parenthetically*

Cumulative dose (mg/kg)	Compound	Ventricular ectopic beats: Before (%)	Ventricular ectopic beats: Maximum change (%)	Ventricular ectopic beats: Maximum change (min after inj.)	Ventricular ectopic beats: 50% return (min)	Mean arterial pressure: Before (mm Hg)	Mean arterial pressure: After† (% change)	Atrial rate: Before (beats/min)	Atrial rate: After† (% change)
0·5	Saline*	76·3±4·7	−6·5±4·6	3·3±3·3	6·7±3·3	110·0±8·7	—2·2±8·1	124·7±8·4	−4·5±2·0
	(±)-propranolol	78·7±8·7	−29·4±21·8	13·3±8·8	7·5±3·5	100·3±1·7	−3·7±3·3	123·7±28·9	−6·4±5·5
	(±)-alprenolol	89·3±6·1	—58·3±21·0§	11·7±9·3	5·0±0·0	101·7±4·2	+7·0±6·1	126·7±5·7	+2·7±5·3
	(−)-alprenolol	76·3±10·2	−41·9±18·0	1·7±1·7	15·0±7·6	86·3±9·2	+18·0±12·5	96·3±4·9	+21·9±3·4
	(+)-alprenolol	84·7±6·6	−17·1±6·5	13·3±6·7	10·0±0·0	101·7±6·0	+3·9±6·5	122·0±6·1	+2·2±3·4
1·5	Saline*	72·7±1·8	−21·1±14·8	13·3±8·3	5·0±0·0	106·7±10·9	+7·8±8·2	112·0±5·8	+12·9±10·2
	(±)-propranolol	78·7±4·4	−35·4±20·1	3·3±3·3	6·7±1·7	96·7±1·7	+3·5±3·5	107·0±21·5	+6·6±5·5
	(±)-alprenolol	73·0±14·0	−71·5±14·7§	0·0±0·0	5·0±0·0	100·0±2·9	−6·8±3·4	123·7±4·6	0·0±0·0
	(−)-alprenolol	72·3±9·8	−54·3±24·2	6·7±6·7	8·3±1·7	93·3±9·3	−10·0±10·0	93·3±6·6	+0·2±15·2
	(+)-alprenolol	86·7±3·2	−18·9±7·6¶	3·3±3·3	13·3±3·3	105·0±7·6	−6·6±4·7	117·7±6·2	−4·1±5·6
3·5	Saline*	82·3±7·8	−26·2±5·7	6·7±6·7	5·0±0·0	116·7±8·3	−4·7±4·4	133·0±10·0	−10·6±4·7
	(±)-propranolol	59·3±15·3	−32·6±22·0¶	5·0±2·9	10·0±0·0	101·7±3·3	+5·1±3·0	109·7±23·3	+4·4±3·2
	(±)-alprenolol	85·0±11·5	−98·3±1·7§	1·7±1·7	8·3±1·7	93·3±4·4	+4·0±13·4	125·0±3·6	−1·5±6·3
	(−)-alprenolol	58·0±25·1	−48·9±26·8¶	3·3±3·3	8·3±1·7	81·7±9·3	−4·2±6·0	97·3±5·9	+20·1±2·8
	(+)-alprenolol	80·0±3·5	−40·1±23·8¶	1·7±1·7	6·7±1·7	101·7±8·8	−2·5±4·3	117·3±1·8	+5·7±3·1
7·5	Saline*	76·7±7·7	−11·3±6·6	3·3±3·3	8·3±1·7	113·3±6·7	−10·3±6·0	113·7±10·5	−0·9±8·0
	(±)-propranolol	73·7±8·4	−94·9±1·2§	0·0±0·0	16·7±3·3	95·0±5·8	0·0±5·5	103·3±18·3	+15·8±14·0
	(±)-alprenolol	58·3±21·4	−99·1±0·9§	1·7±1·7	46·7±36·8	105·0±11·5	−12·4±12·2	117·3±6·6	+2·5±2·5
	(−)-alprenolol	72·0±3·5	−100·0±0·0§	2·3±2·3	40·7±21·2	78·3±11·7	+1·7±7·5	112·0±5·3	+9·5±7·1
	(+)-alprenolol	77·7±9·2	−78·4±8·5§	6·7±6·7	6·7±1·7	98·3±6·7	−11·7±11·7	122·0±5·3	−3·1±10·8
15·5	Saline*	71·7±5·2	−11·5±23·9	13·3±8·8	13·3±8·8	115·0±2·9	0·0±0·0	111·7±9·9	+5·7±10·8
	(±)-propranolol	80·7±10·0	−100·0±0·0§	0·0±0·0	38·3±14·8	98·3±3·3	−21·2±23·6	107·0±20·1	−13·5±16·7
	(±)-alprenolol (2)	44·5	−100·0 §	0·0	20·0>60·0	82·5	−5·7	114·5	+21·9
	(−)-alprenolol	60·0±15·1	−99·1±0·9§	0·0±0·0	45·0±0·0	85·0±13·2	−4·0±6·2	105·0±7·9	+30·5±14·5
	(+)-alprenolol	69·0±9·0	−100·0±0·0§	0·0±0·0	55·0±18·0	106·7±6·7	−11·4±12·1	114·7±6·4	+10·1±5·8
31·5‡	Saline (2)	70·7	−5·0	10·0	5·0	103·3	+2·7	112·5	−2·5
	(±)-propranolol (2)	67·0	−100·0	0·0	—	100·0	−39·7	99·5	+14·1
	(±)-alprenolol (1)	58·0	−100·0	0·0	—	80·0	−12·5	102·0	+15·7
	(−)-alprenolol (1)	70·0	−100·0	0·0	—	70·0	−35·8	99·0	+31·4
	(+)-alprenolol (2)	67·0	−100·0	0·0	—	95·0	−25·5	122·0	+10·5

* 5 ml isotonic saline.
† Values observed at the time of maximum change in the incidence of ventricular ectopic beats.
‡ Excluded from statistical analysis.
Comparisons significant at the 0·05 level (Lindquist type I analysis of variance) are indicated as follows:
§=saline vs. any other compound.
¶=(±) alprenolol vs. (±)-propranolol, (−)-alprenolol or (+)-alprenolol.

other drugs. The arrhythmia was abolished immediately following cumulative doses of 3·5 mg/kg of (±)-alprenolol, 7·5 mg/kg of (±)-propranolol and (−)-alprenolol and by 15·5 mg/kg of (+)-alprenolol. The duration of the antiarrhythmic effect varied considerably and was usually brief following the lower doses as indicated by the time required for half of the suppressed ectopic beats to return. After the total dose of 15·5 mg/kg the duration was about 45 min for each compound. None of the animals survived treatment with 31·5 mg/kg.

Effect of atrial rate

At the time of maximum antiarrhythmic activity, there were no statistically significant differences in atrial rate among the compounds studied (Table 1).

Effect on mean arterial pressure

Following cumulative doses up to 15·5 mg/kg there were no significant differences between the various groups with respect to changes in mean arterial blood pressure during the period of maximum suppression of ventricular beats (Table 1). Cumulative doses of 31·5 mg/kg of (±)-propranolol, (±)-, (−)-, and (+)-alprenolol resulted in a precipitous fall in arterial pressure (Table 1, Fig. 2).

Additional effects

Cumulative doses up to 3·5 mg/kg of the four test drugs caused no grossly observable side effects but 7·5 and 15·5 mg/kg resulted in some instances of lip-licking, emesis and/or head tremors. A cumulative dose of 31·5 mg/kg was invariably lethal.

Discussion

The mechanism by which β-adrenoceptor blocking agents exert their antiarrhythmic effect depends on the nature of the arrhythmia involved. In addition to their antiadrenergic activity, many of these drugs have local anaesthetic and "quinidine-like" properties (Åblad *et al.*, 1967a; Morales-Aguilera & Vaughan Williams, 1965; Parmley & Braunwald, 1967) which could account for their effectiveness against some types of arrhythmias. Resolution of these compounds into stereoisomers having equal cardiodepressant activity but widely different β-adrenoceptor blocking potencies (Åblad *et al.*, 1967a; Howe, 1963; Howe & Shanks, 1966; Parmley & Braunwald, 1967) has made it possible to investigate the significance of β-adrenoceptor blocking activity in the suppression of various arrhythmias. Thus, in animals, abolition of hydrocarbon-anaesthetic arrhythmias was demonstrated to be *via* specific β-adrenoceptor blockade (Howe & Shanks, 1966; Lord *et al.*, 1968) while antagonism of ouabain-induced ventricular tachycardia was unrelated to this property (Duce *et al.*, 1967; Howe & Shanks, 1966; Lucchesi, 1965).

The present experiments have shown that when administered in sufficiently high intravenous doses, (±)-propranolol, (±)-, (−)-, and (+)-alprenolol can suppress arrhythmias produced in the dog by coronary artery ligation. The dose of the racemic compounds and (−)-alprenolol required to abolish these arrhythmias was less than that of (+)-alprenolol but much larger than necessary to produce

blockade of the chronotropic and inotropic responses to isoprenaline (Åblad *et al.*, 1967a). It is apparent that the antiarrhythmic effects exerted by these substances was unrelated to their ability to block the β-adrenoceptors. The results are in agreement with other studies in dogs which have shown that β-adrenoceptor blockade (Shanks & Dunlop, 1967; Somani & Lum, 1965; Madan, Mishra & Khanna, 1969), pre-treatment with reserpine (Maling, Cohn & Highman, 1959) or prior cardiac sympathectomy (Harris, Estandia & Tillotson, 1951) has little influence on the spontaneous ventricular ectopic rhythm which occurs 24 h after experimental acute infarction.

In man, sympathetic blockade does have some beneficial effect against certain ventricular arrhythmias (Anthony *et al.*, 1969; Howitt, 1968; Linko *et al.*, 1967; Linko, Ruosteenoja & Siitonen, 1968; Rowlands, 1965; Stock & Dale, 1963). It effectively suppresses the arrhythmia in some patients with acute myocardial infarction while in others it has no effect (Sowton, 1968). In those cases where sinus rhythm was restored by β-adrenoceptor blockade the arrhythmias may have been associated with an augmented catecholamine release due to anxiety and apprehension (von Euler, 1964). In the dog, sympathetic tone is apparently not a contributing factor in the genesis of the delayed arrhythmias which accompany myocardial infarction.

Since alprenolol (Åblad *et al.*, 1967a) and propranolol (Parmley & Braunwald, 1967) both have a myocardial depressant action apart from their effects on β-adrenoceptors it is possible that this property was responsible for the antiarrhythmic activity observed in the present experiments.

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