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Anti-arrhythmic, local anaesthetic, and adrenergic blocking activity of some β-receptor antagonists

KELD HERMANSEN

Research Division of Pharmacia AS Vanløse, Copenhagen, Denmark

1. The antagonistic effect of the β-receptor blocking compounds propranolol, Ph QA 33 and INPEA on ouabain-induced cardiac fibrillations in guinea-pigs was compared with their local anaesthetic and β-receptor blocking properties.

2. All three compounds were found capable of increasing the tolerance to ouabain and of reversing ouabain-induced fibrillations, the ED50 being 0.3 mg/kg intravenously, 0.5 mg/kg intravenously, and 1.5 mg/kg intravenously, respectively for propranolol, Ph QA 33 and INPEA.

3. Propranolol and Ph QA 33 were found to be moderate to strong local anaesthetics while INPEA had a considerably weaker though significant effect.

4. The order of potency as β-receptor blocking compounds was propranolol $\geq$ Ph QA 33 $\gg$ INPEA, the latter compound being less than 1% as active as propranolol.

5. Despite the surprising finding that INPEA was effective against non-catecholamine-induced arrhythmias, the results support the general assumption that the anti-arrhythmic effect of β-receptor blocking compounds is related to their local anaesthetic action rather than to their β-blocking ability.

Since the work by Lucchesi (1965) on the dextro and racemic form of pronethalol, several investigations have shown that the effect of β-adrenergic blocking agents on non-catecholamine-induced arrhythmias is, to a large extent, unrelated to their β-receptor blocking action (Howe & Shanks, 1966). The unspecific anti-arrhythmic effect of β-blocking compounds is now assumed to be due chiefly to their quinidine-like or local anaesthetic action, a property common to most β-blocking agents.

This assumption has been justified by the observations of Sekiya & Vaughan Williams (1963) and Vaughan Williams (1966) who used intracellular microelectrode techniques on isolated rabbit atria to demonstrate that the electrophysiological changes induced by pronethalol and propranolol were similar to those observed after quinidine. Furthermore, the importance of local anaesthetic activity was emphasized by Somani & Lum (1966), who found that the two β-blocking agents, 4-(2-isopropylamino-1-hydroxyethyl)-methanesulfonanilide HCl (MJ 1999), and 2-isopropylamino-1-(*p*-nitrophenyl) ethanol, HCl (INPEA), both reported to be

devoid of local anaesthetic action, were ineffective against ouabain-induced arrhythmias. Recently the association between anti-arrhythmic and local anaesthetic activity and the dissociation between the former property and β-receptor blockade has been questioned by Barret & Cullum (1968). They found that although the two optical isomers of propranolol had similar local anaesthetic potency, (−)-propranolol, which is by far the most potent β-receptor blocker, was significantly more active than (+)-propranolol against ouabain-induced arrhythmias. They concluded that local anaesthetic properties are essential for unspecific anti-arrhythmic activity but that β-blockade may potentiate this effect.

The aim of the present investigation was to study the relationship between anti-arrhythmic, local anaesthetic and β-receptor blocking effect further by using three β-blocking agents: propranolol, 1-(isopropylamino)-3-(*o*-phenoxyphenoxy)-2-propanol, HCl (Ph QA 33) (Hermansen, 1968), and INPEA. These substances were found suitable for the study because of a decreasing order of local anaesthetic potency. In a preliminary screening test propranolol was three times more active than Ph QA 33, while INPEA is reported to be devoid of local anaesthetic action (Murmann, Saccani-Guelfi & Gamba, 1966).

Methods

Drugs

The following compounds were used: (±)-(isopropylamino)-3-(*o*-phenoxyphenoxy)-2-propanol hydrochloride·½ H_2O (Ph QA 33) containing 86.9% free base; (±)-propranolol hydrochloride (I.C.I.) containing 87.7% free base, (±)-2-isopropylamino-1-(*p*-nitrophenyl) ethanol hydrochloride (INPEA, Selvi & Co., Milano) containing 86.0% free base; (±)-adrenaline bitartrate, (±)-isoprenaline sulphate, ouabain, procaine hydrochloride and tetracaine hydrochloride. The compounds were dissolved in saline at the required concentration. All doses and concentrations mentioned in the text refer to the salts except for adrenaline which is expressed in terms of the base.

Anti-arrhythmic effect

The effect of the compounds on ouabain-induced fibrillations was investigated by a modification of the method of Sekiya & Vaughan Williams (1963). Male guinea-pigs weighing from 300 to 650 g were anaesthetized with urethane (1.5 g/kg intraperitoneally) and artificially respired. Ouabain was infused intermittently into the jugular vein by means of an infusion pump connected to a laboratory timer. The concentration of ouabain was 50 μg/ml. and the infusion cycle arranged so that 4 μg was infused during a period of 30 sec followed by an interruption of 1.5 min. Thus 4 μg ouabain was infused during the 2 min cycle—that is 2 μg/min. The infusion was made intermittent in order to allow accurate recordings of the fibrillatory and lethal dose levels of ouabain. The e.c.g. was obtained with bipolar leads according to Schinzel (1933).

The dose of ouabain infused was fixed to 2 μg/min and not varied according to the weight of the animals. Thus the doses/kg per min varied from 3.1 to 6.7 μg of ouabain. A statistical analysis showed, however, that the antifibrillatory and

fatal doses were independent of the dose of ouabain infused in μg/kg per min within the dose range mentioned. During the infusion of ouabain the typical changes in heart function—bradycardia, ventricular rhythm, etc.—were observed, but only the minimal dose necessary to cause fibrillations and the fatal dose were recorded. The difference between these two doses was calculated after the experiment and is shown in the sixth column of Table 1. The compounds to be tested for antifibrillatory effect were injected intravenously immediately after the fibrillations were manifest. Because of the narrow interval between the onset of fibrillations and cardiac arrest, the exact time for injection of the test compound was critical. Animals not showing definite fibrillations before death were omitted. If the treatment caused a complete restoration to normal sinus rhythm the test dose was regarded as effective and recorded in the seventh column of Table 1. All doses (0.1–1 mg/kg) were given by rapid intravenous injection in the jugular vein, except the dose of 3 mg/kg which was administered at a rate of 1 mg/kg per min. The control group consisted of eighteen guinea-pigs, the test groups of five or ten animals.

Test for local anaesthetic effect

1. Surface anaesthetic effect

The test was carried out on male guinea-pigs weighing between 300 and 800 g by a modification of the method described by Herr (1958). The test solutions were instilled in the conjunctival sac in different concentrations and left there for 1 min. Five minutes later the corneal anaesthesia was measured by applying a pressure of 1 g by means of a test hair. This procedure was repeated five times in rapid sequence and if no blinking reflex was elicited by this procedure, corneal anaesthesia was regarded to be present. The test was made objective by keeping the observer unaware of the identity of the solutions tested. Each concentration was tested on twenty eyes.

2. Conduction anaesthetic effect

Male mice of the NMRI strain weighing from 18–25 g were used and the method employed was essentially that described by Bianchi (1956).

Each concentration of the test compound was tested on twenty mice.

Tests for β-adrenergic blocking effect

1. Contraction rate, isolated guinea-pig atrium

The method was the same as described previously (Hermansen, 1968). In preliminary experiments the antagonistic effect of Ph QA 33, propranolol and INPEA on the adrenaline-induced tachycardia was estimated very roughly. Next cumulative dose-response curves for adrenaline were constructed in the absence and then in the presence of a fixed concentration of either antagonist. This concentration was chosen separately for each compound so the increase of the ED50 for adrenaline was of the same order. Each point necessary for construction of the dose-response curve represented the mean of four determinations.

2. Blood pressure, anaesthetized rat

The method used was the same as described previously (Hermansen, 1968).

Acute intravenous toxicity, guinea-pig

In order to obtain an impression of the relative toxicity of the test compounds the lethal dose was determined in the same species and in the same experimental conditions—that is, urethane anaesthesia (1.5 g/kg intraperitoneally) as employed during the anti-arrhythmic studies. The test compounds were infused intravenously at a rate of 1 mg/kg per min until cardiac arrest occurred. It proved impossible to determine the lethal dose of INPEA at the above-mentioned rate of injection with a reasonable volume of infusate (<25 ml.) so this was increased to 5 mg/kg per min. Five guinea-pigs were used in each group and the LD100 expressed as the mean ±S.E.M.

Results

Anti-arrhythmic effect of Ph QA 33, propranolol and INPEA

The effect of Ph QA 33, propranolol and INPEA, each at three different dose levels, on ouabain-induced fibrillations was investigated. Figures 1 and 2 show typical e.c.g. tracings from experiments with the three compounds. Figure 1a and b illustrate the antifibrillatory effect of Ph QA 33 1 mg/kg and propranolol 0.5 mg/kg intravenously. Both compounds caused a complete abolition of the ventricular fibrillations as illustrated in parts 3 and 4 of Fig. 1, and return to normal sinus rhythm. Similarly Fig. 2a demonstrates that INPEA 1 mg/kg was only partially effective in abolishing the fibrillations while INPEA 3 mg/kg (Fig. 2b) completely restored the normal sinus rhythm. Table 1 summarizes all the results. The last column indicates the approximate ED50 values estimated from the percentage of restored animals at each dose level. Ph QA 33 shows a linear dose-

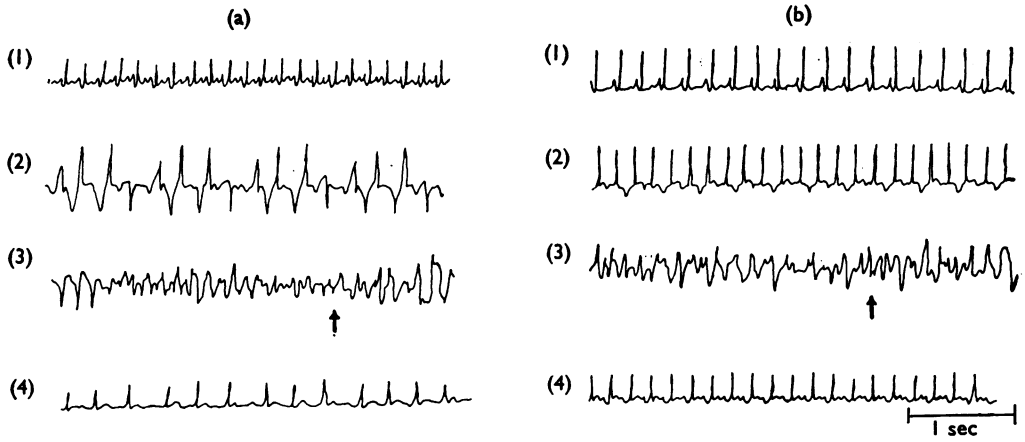

FIG. 1. Effect of Ph QA 33 (a) and propranolol (b) on ouabain-induced cardiac fibrillations in guinea-pigs. At (1) the control e.c.g. is seen. (2) shows the e.c.g. 45 min (a) and 62 min (b) after the start of the ouabain infusion. At (3) fibrillations occurred; at the arrows Ph QA 33 1 mg/kg (3a) and propranolol 0.5 mg/kg (3b) were given intravenously. (4) shows the e.c.g. 7 min (a) and 5 min (b) after drug administration (ordinate: 0.5 cm=1 mV).

response relationship (column 7) giving an ED50 of 0.5 mg/kg while the maximal antifibrillatory effect of propranolol was obtained at 0.5 mg/kg. When the dose was increased to 1 mg/kg no further increase in antifibrillatory effect occurred. The ED50 was estimated to be 0.3 mg/kg while the ED50 for INPEA was 1–3 mg/kg (approximately 1.5 mg/kg).

The observed effect of Ph QA 33, propranolol and INPEA on ouabain-induced cardiotoxicity could also be demonstrated by an increased tolerance to ouabain. Thus column 6 in Table 1 shows that the amount of ouabain necessary to cause cardiac arrest after fibrillations had emerged was significantly increased after drug treatment.

To ensure that the observed increase in tolerance to ouabain was not due to irrelevant factors such as different fibrillatory dose levels of the groups, the influence of this parameter on the amount of extra ouabain required to cause cardiac arrest after fibrillations had occurred, was statistically analysed. The control group ($n=18$) was therefore divided into two groups, one consisting of nine guinea-pigs showing fibrillations at a dose level less than 277 μg/kg ouabain and another consisting of nine animals with a minimal fibrillatory dose above 277 μg/kg. The mean fibrillatory dose in the first group was 212 μg/kg, in the second group 342 μg/kg. The fatal doses in the two groups were 236 and 357 μg/kg respectively. The difference between the fatal and fibrillatory dose was thus 24 ± 2 and 15 ± 3 μg/kg (S.E.M.) in the two groups. These two figures are significantly different ($P<0.05$), which means that the lower the minimal fibrillatory dose then the larger amount of extra ouabain required to cause cardiac arrest.

As a consequence of these considerations the increased tolerance to ouabain illustrated by the figures in column 6 of Table 1 can only be ascribed to drug treatment if the corresponding minimal fibrillatory dose (column 4) is not significantly lower than the control value of ouabain (277 ± 18 μg/kg). This requirement was fulfilled for all the test groups and it can therefore be stated that the increases in the doses of ouabain required to cause cardiac arrest shown in column 6 of Table

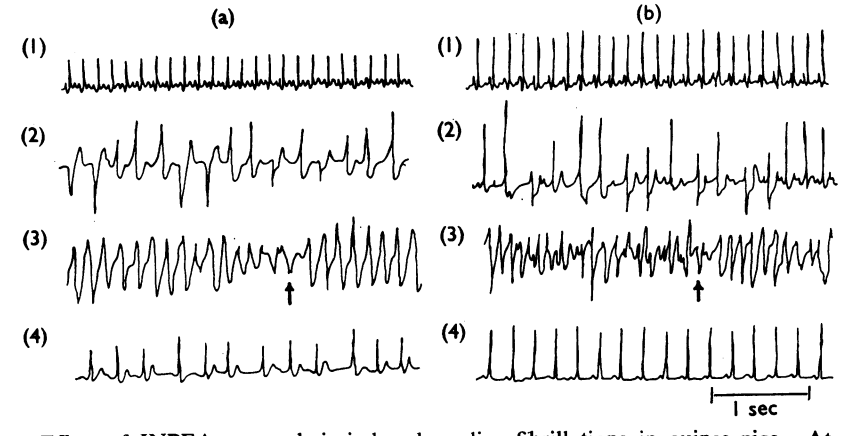

FIG. 2. Effect of INPEA on ouabain-induced cardiac fibrillations in guinea-pigs. At (1) the control e.c.g. is recorded. (2) shows the e.c.g. 40 min (a) and 48 min (b) after the start of the ouabain infusion. At (3) fibrillations occurred; at the arrows INPEA 1 mg/kg (3a) and 3 mg/kg (3b) was given intravenously. (4) shows the e.c.g. 7 min (a) and 8 min (b) after drug administration respectively (ordinate: 0·5 cm=1 mV).

1 must be caused by drug treatment. The group which received propranolol 0.3 mg/kg showed a signicantly higher fibrillatory dose level (364 ± 18 μg/kg) than the control group, but this would only tend to make it less sensitive to further infusion of ouabain.

The results in column 6 demonstrate a clear dose dependent increase of the tolerance to ouabain. The lowest dose causing a significant increase ($P<0.05$) was for Ph QA 33 0.3 mg/kg, for propranolol 0.1 mg/kg and for INPEA 1.0 mg/kg intravenously. The lack of dose response relationship of propranolol as to antifibrillatory effect which was observed at 0.5 and 1.0 mg/kg (column 7) was not seen when the antagonistic effect of this substance was expressed in terms of tolerated dose of ouabain. As column 6 of Table 1 shows this increased with the dose a linear fashion.

Local anaesthetic effect of Ph QA 33, propranolol and INPEA

1. Effect of topical application on the guinea-pig cornea

Figure 3 shows the results from the surface anaesthetic test obtained with Ph QA 33, propranolol and INPEA plotted on a semi-logarithmic scale. Procaine and tetracaine were included as reference substances. As Fig. 3 shows, procaine was ineffective as a surface anaesthetic as is well known (Herr, 1958) while the ED50 for tetracaine was 2.7 mg/ml. Ph QA 33 and propranolol were equally active, the ED50s being 7.0 and 7.5 mg/ml. respectively. INPEA was found ineffective in concentrations of 40 and 100 mg/ml. The latter finding is in accordance with previous observations (Somani & Lum, 1965 ; Murmann *et al.*, 1966) using the rabbit cornea as test organ.

TABLE 1. *Effect of Ph QA 33, propranolol, and INPEA on ouabain-induced cardiotoxicity*

Compound	mg/kg i.v.	No. of animals	Ouabain μg/kg i.v. causing: Fibrillations	Ouabain μg/kg i.v. causing: Cardiac arrest	Difference between fatal and fibrillatory dose Ouabain μg/kg i.v.	Antifibrillatory effect: % of restored animals	Antifibrillatory effect: ED50 mg/kg i.v.
Control		18	277±18	297±17	20±2	0	
Ph QA 33	0·1	5	283±18	318±15	35±10	20	0·5
	0·3	10	276±25	320±24	43±9*	30	
	1·0	10	239±17	355±14	116±14*	90	
Propranolol	0·1	5	232±30	269±32	37±7*	20	0·3
	0·3	10	364±18	421±18	57±11*	50	
	0·5	10	238±18	308±22	70±13*	60	
	1·0	10	291±24	382±18	91±15*	60	
INPEA	0·3	5	297±23	322±19	25±5	0	1–3
	1·0	5	262±33	319±20	57±17*	20	
	3·0	5	229±23	330±31	101±16*	100	

The dose of ouabain which caused fibrillations and cardiac arrest is expressed as the mean ± S.E.M. The compounds were given by rapid intravenous injection immediately after fibrillations had emerged. The dose of ouabain necessary to cause cardiac arrest after fibrillations had occurred is shown in column 6.

* Significantly different from the control value ($P<0·05$).

2. Effect of subcutaneous administration in the mouse

Figure 4 demonstrates the local anaesthetic effect of Ph QA 33, propranolol and INPEA after subcutaneous administration in the mouse tail. Procaine was included as a standard of reference. The figure shows clearly that propranolol is by far the most active compound with an ED50 of about 1.15 mg/ml. Ph QA 33 and procaine were found approximately equally potent (ED50: 3.1 to 3.5 mg/ml.). This corresponds to a local anaesthetic effect about one-third of that of propranolol.

INPEA had a weak but significant and dose dependent local anaesthetic effect with an ED50 of about 18 mg/ml. Thus it is about 15 times weaker than propranolol and 5 times weaker than Ph QA 33. The latter finding was surprising and

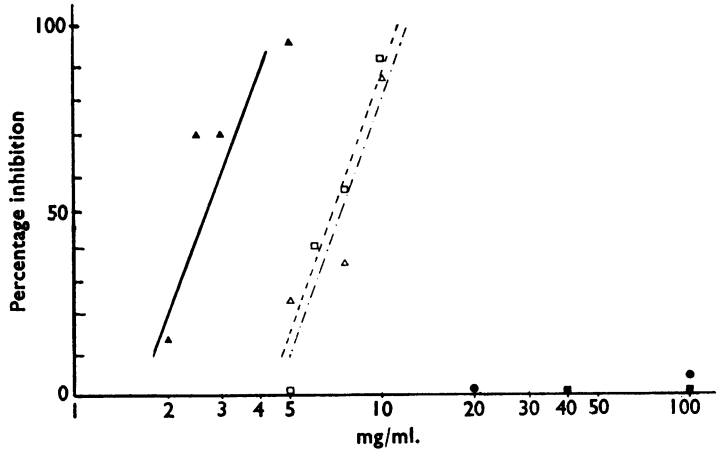

FIG. 3. Surface anaesthetic effect of Ph QA 33 (□- - -□), propranolol (△-·-·-△), INPEA (■), tetracaine (▲——▲), and procaine (●) on the guinea-pig cornea. Each point represents the mean result from twenty determinations.

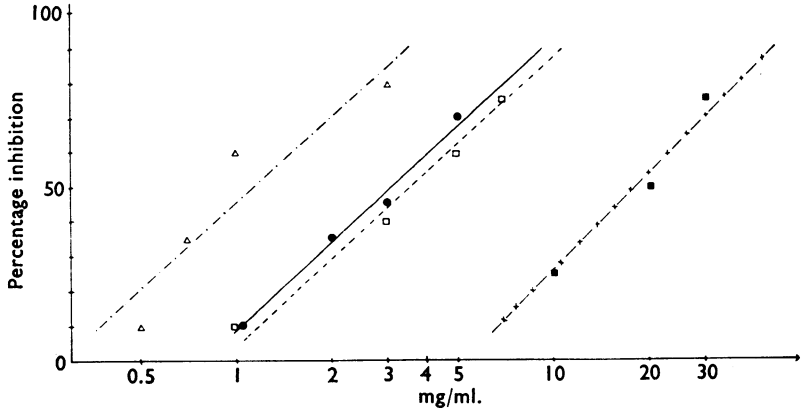

FIG. 4. Conduction anaesthetic effect of Ph QA 33 (□- - -□) propranolol (△-·-·-△), INPEA (■-x-x-■) and procaine (●——●) on the mouse tail. Each point represents the mean result from determinations on twenty mice.

incompatible with that of Murmann *et al.* (1966), who only obtained 15% anaesthesia with a 3% solution of INPEA. Fig. 4 shows that we obtained about 70% anaesthesia with the same concentration.

β-receptor blocking effect of Ph QA 33, propranolol and INPEA

1. Effect on the adrenaline-induced increase in contraction rate of atria in vitro

Figure 5 shows that incubation of the atria in concentrations of 5×10^{-8}, 1.5×10^{-8} and 1.5×10^{-6} g/ml. of Ph QA 33, propranolol and INPEA respectively caused a parallel shift of the dose-response curves to the right indicating a competitive antagonistic effect on the chronotropic action of adrenaline.

Figure 5 shows that INPEA 1.5×10^{-6} g/ml. caused a smaller increase of the ED50 to adrenaline than Ph QA 33 and propranolol 5×10^{-8} and 1.5×10^{-8} respectively. The β-receptor blocking activity of INPEA *in vitro* therefore seems to be less than 1% of that of propranolol. The results also showed that propranolol was about three times more active than Ph QA 33 in this test.

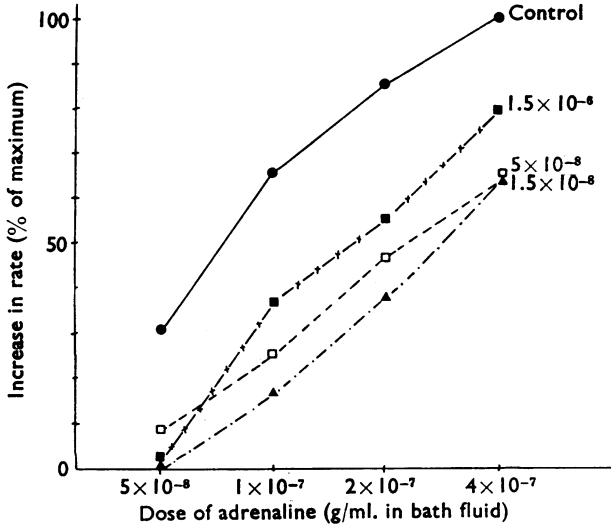

FIG. 5. Effect of Ph QA 33 (□- - -□), propranolol (▲- · - · -▲) and INPEA (■ - x - x - ■) on adrenaline-induced tachycardia. Guinea-pig atria *in vitro*. The points necessary for construction of the cumulative dose-response curves represent the mean of determinations. For further description see text.

TABLE 2. *Acute intravenous toxicity of Ph QA 33, propranolol and INPEA in urethane-anaesthetized guinea-pigs (mean±S.E.M.)*

Compound	LD100 mg/kg i.v.	ED50 antiarrhythmic effect/LD100 i.v.
Ph QA 33	20·3±1·5	1 : 47
Propranolol	14·2±1·1	1 : 40
INPEA	98·5±11·4	1 : 65

2. Effect on the isoprenaline-induced fall in blood pressure in the rat

Administration of INPEA 1 mg/kg intravenously caused a 13% ($n=4$) reduction of the isoprenaline-induced fall in blood pressure. 3 mg/kg caused a complete abolition ($n=3$), indicating that the ED50 for INPEA was between 1 and 3 mg/kg. Previous experiments with Ph QA 33 and propranolol showed ED50s of 7.5 μg/kg and 8 μg/kg (Hermansen 1968) indicating that the antagonistic effect of INPEA on the isoprenaline-induced blood pressure fall was less than 1% of that of Ph QA33 and propranolol. The low activity of INPEA in this test has also been demonstrated previously by Teotino, Polo Friz, Steis & Della Bella (1963), who needed INPEA 10 mg/kg intravenously in order to obtain a complete abolition of the isoprenaline response.

Acute intravenous toxicity of Ph QA 33, propranolol and INPEA, guinea pigs

Table 2 shows the lethal dose of Ph QA 33, propranolol and INPEA estimated under the same experimental conditions in which the anti-arrhythmic effect was assessed. The LD100 of INPEA is not directly comparable with that of Ph QA 33 and propranolol because the rate of injection of the latter compound was 1 mg/kg per min. At this rate it was impossible to determine the LD100 for INPEA as mentioned previously. INPEA was therefore injected at a rate of 5 mg/kg per min. The results show that INPEA is considerably less toxic than both Ph QA 33 and propranolol. The last column in Table 2 gives the relation between anti-arrhythmic effect and intravenous LD100, indicating that the ratio between the anti-arrhythmic and toxic level of INPEA may be more favourable than that of the two other compounds. The ratio does not give any impression as to the specificity of the compounds as anti-arrhythmics because the first parameter is tested on ouabain-loaded animals, the latter on unloaded ones.

Discussion

The finding that Ph QA 33 was effective against ouabain-induced arrhythmias was not surprising in view of the close pharmacological relationship to propranolol, the anti-arrhythmic properties of which are well established (Hermansen, 1968; Lucchesi, Whitsitt & Stichney, 1967). This indicates that Ph QA 33 might also be a potential anti-arrhythmic in the clinic.

The anti-arrhythmic potency of Ph QA 33 was assessed to be about half that of propranolol, while the surface anaesthetic action was equal to and the conduction anaesthetic action about one-third of that of propranolol. Thus the order of anti-arrhythmic effect of these two compounds fits well with the general assumption that the local anaesthetic action of β-blocking agents is a crucial factor behind the antagonism of cardiac irregularities.

Particularly surprising was the observation that INPEA was capable of reversing fibrillations brought about by ouabain. INPEA has previously been reported to be effective in preventing adrenaline and methylchloroform-adrenaline-induced arrhythmias in the intact dog (Somani *et al.*, 1965), in halothane-adrenaline arrhythmias in the dog heart-lung preparation (Somani *et al.*, 1966) and against fibrillations caused by hypothermia in the cat (Nielsen & Owman, 1968). These are all conditions involving adrenergic mechanisms.

On the contrary INPEA was found ineffective against non-catecholamine-induced arrhythmias such as cardiac rhythm disturbances induced by coronary ligation or ouabain infusions in the dog heart-lung preparation, in intact dogs (Somani *et al.*, 1965, 1966) as well as in cats (Levitt, Raines, Moros & Standaert, 1968).

The latter authors were able to increase the lethal dose of ouabain by large doses of INPEA (15 mg/kg intravenously), but did not succeed in reversing ventricular tachycardia. The failure of INPEA to antagonize non-catecholamine-induced cardiac irregularities such as ouabain-arrhythmias has been explained by the reported lack of local anaesthetic effect and has actually been used in the argument for the lack of correlation between anti-arrhythmic and β-receptor blocking properties (Somani *et al.*, 1965 ; Murmann *et al.*, 1966). In accordance with our observation that INPEA does indeed reverse ouabain fibrillations, we also found the substance to possess weak but definite local anaesthetic properties when injected subcutaneously. As to the anti-arrhythmic effect of INPEA the discrepancy between previous observations and our findings may be accounted for by different choice of species and variations in the experimental method.

Although our results obtained with INPEA are incompatible with those previously published, the observations presented here confirm the proposed relationship between unspecific anti-arrhythmic and local anaesthetic action. Thus if the lack of surface anaesthetic effect of INPEA is disregarded, which may be justified by the fact that this test involves many irrelevant factors such as poor absorption from the conjunctival sac, etc., then the order of potency of the three compounds as anti-arrhythmics is the same as that as local anaesthetics, namely propranolol>Ph QA 33> INPEA (Table 1, Fig. 4).

In order to clarify the discrepancy between previous work and the present results and to elucidate the mechanism of action of INPEA in cardiac arrhythmias further work is needed employing more elaborate methods.

With regard to the relationship between anti-arrhythmic and β-receptor blocking properties, our results support the view that the antagonistic effect of β-blocking agents on ouabain-induced arrhythmias is independent of their affinity to β-adrenergic receptors. Certainly the order of potency of propranolol, Ph QA 33 and INPEA is the same for the two parameters, but the low activity of INPEA as a β-receptor blocking compound (less than 1% of propranolol) makes it unlikely that this property is responsible for its substantial anti-arrhythmic effect (intravenous ED50 ~1.5mg/kg).

The toxicity data and the ratio between anti-arrhythmic effect and intravenous toxicity in Table 2 indicate that INPEA is considerably less toxic than Ph QA 33 and propranolol. It was not possible to obtain reversal of the fibrillations in more than 60% of the animals by the latter compound in doses of 0.5 to 1 mg/kg intravenously at which propranolol is definitely cardiodepressant in anaesthetized cats (Hermansen, 1968). The question therefore arises as to the specificity of β-receptor blocking agents as anti-arrhythmics. A new approach in this field has been made by the synthesis of the quaternary analogue of propranolol (ICI 46,037), which possesses the same anti-arrhythmic potency as propranolol without the undesirable effects associated with β-adrenergic receptor blockade (Lucchesi & Iwami, 1968). From the same point of view our results indicate that INPEA being a weak β-receptor blocking agent may have advantages to the stronger compounds in the use against non-catecholamine-induced cardiac rhythm disturbances.

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REFERENCES

BIANCHI, C. (1956). A simple new quantitative method for testing local anaesthetics. *Br. J. Pharmac. Chemother.*, **11**, 104–106.

BARRET, A. M. & CULLUM, V. A. (1968). The biological properties of the optical isomers of propranolol and their effects on cardiac arrhythmias. *Br. J. Pharmac.*, **34**, 43–55.

HERMANSEN, K. (1968). Some pharmacological properties of a new β-adrenergic blocking agent 1-(isopropylamino)-3-(o-phenoxyphenoxy)-2-propanol, HCl (Ph QA 33). *Acta Pharmac. Tox.*, **26**, 343–362.

HERR, F. (1958). Zur Frage der Standardisierung der Prüfung von Lokalanästhetica. *Arzneimittel-Forsch.*, **8**, 137–141.

HOWE, R. & SHANKS, R. G. (1966). Optical isomers of propranolol. *Nature, Lond.*, **210**, 1336–1338.

LEVITT, B., RAINES, A., MOROS, D. & STANDAERT, F. G. (1968). Antagonism of ouabain-induced ventricular tachycardia (VT) and death by large doses of N-isopropyl-p-nitro-phenyl ethanolamine (INPEA) in the cat. *Fedn Proc.*, **27**, 348.

LUCCHESI, B. R. (1965). The effects of pronethalol and its dextroisomer upon experimental cardiac arrhythmias. *J. Pharmac. exp. Ther.*, **148**, 94–99.

LUCCHESI, B. R. & IWAMI, T. (1968). The antiarrhythmic properties of ICI 46037, a quaternary analog of propranolol. *J. Pharmac. exp. Ther.*, **162**, 49–59.

LUCCHESI, B. R., WHITSITT, L. S. & STICHNEY, J. L. (1967). Antiarrhythmic effects of beta adrenergic blocking agents. *Ann. N.Y. Acad. Sci.*, **139**, 940–951.

MURMANN, W., SACCANI-GUELFI, M. & GAMBA, A. (1966). Pharmacological properties of 1-(4′-nitrophenyl)-2-isopropylamino-ethanol (INPEA)(R) a new beta-adrenergic receptor antagonist. *Boll. Chim. Farm.*, **105**, 292–300.

NIELSEN, K. C. & OWMAN, C. (1968). Control of ventricular fibrillation during induced hypothermia in cats after blocking the adrenergic neurones with bretylium. *Life Sci., Oxford*, **7**, 159–168.

SCHINZEL, G. (1933). Das Elektrokardiogramm der kleinen Laboratoriumstiere. Dissertation, München.

SEKIYA, A. & VAUGHAN WILLIAMS, E. M. (1963). A comparison of the antifibrillatory actions and effects on intracellular cardiac potentials of pronethalol, disopyramide and quinidine. *Br. J. Pharmac. Chemother.*, **21**, 473–481.

SOMANI, P. & Lum, Bert K. B. (1965). The antiarrhythmic actions of beta adrenergic blocking agents. *J. Pharmac. exp. Ther.*, **147**, 194–204.

SOMANI, P. & LUM, BERT K. B. (1966). Blockade of epinephrine- and ouabain-induced cardiac arrhythmias in the dog heart-lung preparation. *J. Pharmac. exp. Ther.*, **152**, 235–242.

TEOTINO, U. M., POLO FRIZ, L., STEIS, G. & DELLA BELLA, D. (1963). Synthesis and pharmacological properties of some derivatives of p-aminophenylethanolamine. *J. Pharm. Pharmac.*, **15**, 26–33.

VAUGHAN WILLIAMS, E. M. (1966). Mode of action of beta receptor antagonists on cardiac muscle. *Am. J. Cardiol.*, **18**, 399–405.

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