AN EXPERIMENTAL STUDY OF THE β -RECEPTOR BLOCKING AGENTS ON THE CARDIAC PERFORMANCE IN DOGS

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Since the introduction of dichloro analogue of isoprenaline (DCI) by Powell and Slatter (1), several β -receptor blocking agents have been introduced in the present day medicine. Among these, propranolol is being used in various clinical conditions like angina pectoris (2-3), myocardial infarction (4) and ventricular arrhythmias (5-6). Further, propranolol has been used as local anaesthetic in minor surgical procedures (7). However, the clinical usefulness of these agents in various cardiac conditions is limited by the fact that they, some times, induce severe and irreversible cardiac failure. The present study has been done on the heart-lung preparation of the dog with a view to assess the relative myocardial depressant activity of INPEA and propranolol and also to find out some suitable agents which may effectively antagonize the cardiac failure caused by these agents.

METHODS

Modified Starling heart-lung preparation (HLP) was set up in 13 dogs weighing between 10-15 kg, under pentobarbital sodium anaesthesia (35 mg/kg, i.p.). The lungs were ventilated with the atmospheric air by means of Starling's pump. Before opening the chest, about 200 ml of blood was taken out from the left carotid artery in order to minimize bleeding during operative procedure. This blood was defibrinated and was added to the blood obtained from the donor dog.

The mean arterial pressure was set at 80-100 mm Hg and was recorded from the side tubing of the brachio-cephalic cannula on kymograph paper by means of a mercury manometer. The right atrial pressure was recorded with a water manometer. The systemic output (cardiac output minus coronary flow) was adjusted between 300-400 ml/min and was recorded by means of a Weese stromuhr with a stroke volume of 100 ml. The heart rate was recorded by using direct pericardial leads on Sanborn-150 polygraph. The total blood volume during the start of the experiment ranged between 700 to 800 ml of blood. The level of blood reservoir was kept at 12 cm above the heart level. The defibrinated blood was collected a day before the experiment from the bleed-er dog under ether anaesthesia, and was kept at 4°C. The temperature of blood enter-

ing superior vena cava ranged from 37° to 38°C. Half an hour was given to stabilize the heart-lung circulation. The heart rate, cardiac output and temperature of the blood was recorded every two minutes throughout the experiment. The work of the heart was calculated by the formula of Evans and Matsuoka (8). Before the injection of the drug, a competence test was performed by raising the level of venous reservoir to 50 mm (Cr) each time. The competence index (CI) was calculated according to the method of Wollenberger (9) by the following formula:

$$CI = \frac{\text{Increase in level of venous reservoir} - \text{Increase in right atrial pressure}}{\text{Increase in level of venous reservoir}}$$

The competence index in our experiments, before the injection of the drug, ranged from 0.88–1.00. The competence test was repeated after each injection of the drug. Control HLP with an initial competence index of more than 0.88 were found to be stable for at least an hour and a half as judged from repeated competence tests. Preparations with initial competence index lower than 0.88 were discarded from the study as they were found to deteriorate spontaneously.

INPEA and propranolol were dissolved in normal saline at a concentration of 50 mg/ml. The drug solutions were injected slowly into the tubing close to the superior vena cava. The volume of the injection was always kept 1 ml. In control experiments the injection of normal saline (5 ml) produced no significant effect on the performance of the heart. The concentration of the drug per kg of the weight of the HLP i.e. the combined weight of the heart, blood and lung was ascertained. The weight of the lung was taken to be 1/75 of the body weight (10). An attempt was made to reverse the heart failure by isoprenaline and/or strophanthin.

The drugs employed in the present study were: INPEA hydrochloride (Selvi and Co., Italy), propranolol hydrochloride (Imperial Chemical Industries, England), isoprenaline sulphate (Burroughs Wellcome, India) and strophanthin (Sandoz, India).

RESULTS

Effect of INPEA and propranolol was studied on blood pressure, heart rate, cardiac output, right atrial pressure, competence index and work of the heart in HLP of dog. Both INPEA and propranolol produced negative chronotropic and inotropic effects as

TABLE 1. Effect of INPEA on heart-lung preparation (HLP) of dog.

Drug	Dose in mg/kg HLP	Experiments	H.R. min	B.P. mmHg	CO ml/min	RAP mmH ₂ O	Competence index	Work kg M/min
INPEA	0	7	152	92	360	2	0.96	0.43
	45.4	7	142	90	340	7	0.94	0.40
	90.8	7	122	87	311	19	0.82	0.35
	136.2	7	100	82	208	32	0.50	0.22
	179.6	7	72	68	86	49	0.32	0.07
Isoprenaline (5 µg/min for 5 min)		7	164	91	354	4	0.94	0.42

FIG. 1. Competence indices for INPEA. Control value of competence index before administration of INPEA (A). INPEA was administered every 15 minutes in doses per kg heart-lung preparation, 45.4 mg (B), 90.8 mg (C), 136.2 mg (D) and 179.6 mg (E). Note that there is a progressive decrease in the competence index (B to E). At arrow (I) isoprenaline infusion (5 μ g/min for 5 minutes) was given. The competence index after isoprenaline infusion returned almost to control value (F). Vertical lines indicate standard errors.

FIG. 2. Competence indices for propranolol. Control value of competence index before administration of propranolol (A). Propranolol was administered every 15 minutes in doses per kg heart-lung preparation, 45.4 mg (B), 90.8 mg (C) and 136.2 mg (D). Note the marked decrease of competence index at (D). At this stage at arrow (I) isoprenaline infusion (10 μ g/min for 8 minutes) could produce only a little increase in competence index (E). While at arrow (S), infusion of strophanthin 5.0 μ g/min for 5 min brought the competence index to control value (F). Vertical lines indicate standard errors.

FIG. 4. The effect of propranolol on the heart-lung preparation of dog.

The tracings from above downwards are of cardiac output (CO) 100 ml/stroke, arterial pressure (BP), right atrial pressure (RAP) and time. Heart rate (HR) was obtained electrocardiographically and is indicated in figures. For the competence test, venous reservoir was raised to 50 mm (C₁) above control blood supply level and the venous reservoir was lowered to control supply level at (C₂). The control blood supply level was 120 mm above the level of the heart. The triangles 1-3 indicate injections of 46 mg/kg HLP of propranolol each. In the first panel the control competence test indicated a fully competent heart. In the second panel at triangle three (total dose) 138 mg/kg HLP of propranolol produced a marked rise in RAP and reduction of cardiac output. Competence test performed after this (C₁) showed further deterioration of the heart. At arrow 10 μ g/min infusion of isoprenaline was given for 8 minutes. See that it could not reverse the heart failure. At this stage strophanthin 5 μ g/min infusion was given for 5 minutes. Note that this effectively reversed the cardiac failure as evidenced by the return of HR, RAP and CO to almost control values.

is evidenced by slowing of the heart rate, lowering of the blood pressure, reduction in cardiac output, work of the heart and competence index and a rise of right atrial pressure (Table 1). The dose of INPEA required to reduce the competence index from 0.9 to 0.2 was found out by interpolation or extrapolation (11), to the 196.4 mg/kg HLP and that of propranolol required to reduce the competence index from 0.9 to 0.2 was 138.2 mg/kg HLP. Thus, propranolol was approximately one and a half times more depressant to myocardium than INPEA.

The mean competence indices with standard errors at various dose levels of INPEA and propranolol have been plotted in Figs. 1 and 2 respectively. With increasing doses, there was a progressive fall in the competence indices. The depression of myocardium was significantly greater with propranolol than with INPEA ($P < 0.01$) when the two drugs were given in the same dose 90.8 mg/kg HLP (Figs. 1 and 2-C). Furthermore, the heart failure induced by INPEA could be successfully reversed by isoprenaline infusion (5 μ g/min for 5 minutes) (Fig. 3 and Table 1). On the other hand, the failure induced by propranolol could not be overcome by isoprenaline infusion (10 μ g/min for 8 minutes). However, strophanthin (5 μ g/min for 5 minutes) successfully reversed

FIG. 3. The effect of INPEA on the heart-lung preparation of dog. The tracings from above downwards are of cardiac output (CO) 100 ml/stroke, arterial pressure (BP), right atrial pressure (RAP) and time. Heart rate (HR) was obtained electrocardiographically and is indicated in figures. For the competence test venous reservoir was raised to 50 mm (C_1) above the control blood supply level and the venous reservoir was lowered to control supply level at (C_2). The control blood supply level was 120 mm above the level of the heart. The triangles 1-4 indicate injections of 45 mg/kg HLP of INPEA each. In the left panel the control competence test indicated a fully competent heart. At the triangle 4 (total dose) 180 mg/kg HLP of INPEA produced a marked rise in RAP and reduction of CO. Competence test performed after this (C_1) showed further deterioration. At this stage 5 μ g/min infusion of isoprenaline for 5 minutes reversed the heart-failure as is evidenced by reversal of HR, CO, and RAP to almost control values.

TABLE 2. Effect of propranolol on heart-lung preparation (HLP) of dog.

Drug	Dose mg/kg HLP	Experiments	H.R. min	B.P. mmHg	CO ml/min	RAP mmH ₂ O	Competence index	Work kg M/min
Propranolol	0	6	155	94	370	2	0.96	0.45
	45.4	6	136	88	250	11	0.80	0.29
	90.8	6	93	80	144	32	0.41	0.16
	136.2	6	66	62	92	51	0.22	0.07
Isoprenaline (10 μ g/min for 8 min)	—	6	68	65	104	48	0.26	0.08
Strophanthin (5 μ g/min for 5 min)	—	6	125	93	364	3.5	0.94	0.44

the failure induced by propranolol (Fig. 4 and Table 2). The heart rate also increased after strophanthin.

DISCUSSION

β -Receptor blocking agents are being used in clinical practice. However, the therapeutic usefulness of these agents is limited because of their myocardial depressant activity. In the present study, the effect of INPEA and propranolol was studied on blood pressure, heart rate, cardiac output, right atrial pressure, competence index and work of the heart in the HLP of dog. Both these agents were found to decrease heart rate, blood pressure, cardiac output and increase the right atrial pressure, thereby exhibiting a cardiac depressant action. The depressant action of these drugs was quantitatively assessed from the decrease in competence index which is a standard measure of cardiac reserve (12).

The dose of INPEA to reduce the competence index from 0.9 to 0.2 was 196.4 mg/kg HLP whereas that of propranolol was 138.2 mg/kg HLP. Thus propranolol was one and a half times more toxic to the myocardium than INPEA. It is well known fact that adrenergic control of heart is mediated through β -receptors. Therefore, β -receptor blocking agents are most likely to cause myocardial depression which hypothetically should be reversed by known β -agonists. The cardiac failure induced with INPEA was completely reversed by isoprenaline (5 μ g/min infusion for 5 minutes) while that induced with propranolol could only be partially reversed even after higher doses of isoprenaline. However, strophanthin, a direct cardiac stimulant, completely reversed the negative chronotropic effect as well as cardiac failure induced with propranolol. The increase in heart rate observed after strophanthin in the present study, is some what contrary to the usual expectations. Furthermore, Tuttle and Innes (13) also observed that in the presence of isoprenaline, ouabain increased the heart rate in animals where the β -receptors were blocked by pronethalol. The results of the present study indicate that the underlying mechanisms involved in the cardiac failure by INPEA and propranolol are different. As the cardiac failure induced by INPEA was reversed with isoprenaline, a known β -agonist, it seems that INPEA does so by specifically blocking the β -receptors. In the case of propranolol this is not true because cardiac failure could only be reversed

partially with isoprenaline while strophanthin, a direct cardiac stimulant, reversed it completely, showing thereby the involvement of both β -receptor blocking and direct myocardial depressant activities. Similar myocardial depressant activity has been demonstrated by Morales-Aguilera and Vaughan Williams (14) in propranolol using intracellular potential recording techniques. Furthermore, it is suggested that isoprenaline and strophanthin may be used in cases of myocardial depression induced by INPEA and propranolol respectively.

SUMMARY

The relative cardiac depressant activity of two β -receptor antagonists, INPEA and propranolol, was studied on modified Starling heart-lung preparation and an attempt was made to reverse the heart failure induced by these agents with isoprenaline and strophanthin. Both INPEA and propranolol exhibited negative chronotropic and inotropic effects. Propranolol was approximately one and a half times more potent than INPEA in depressing the myocardium. Furthermore, the heart failure induced by INPEA could be successfully reversed by isoprenaline. On the other hand, propranolol induced failure could not be completely antagonized even with higher doses of isoprenaline. Strophanthin, a direct stimulant of myocardium could effectively reverse the cardiac depressant and negative chronotropic effect of propranolol. It is, therefore, concluded that the myocardial depressant action of INPEA is the result of specific β -blockade, whereas that of propranolol is due to β -receptor blockade as well as direct depressant action on the myocardium, the latter is specifically antagonized by cardiac glycoside.

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