EFFECT OF PROPRANOLOL AND [4-(2-ISOPROPYLAMINO-1-HYDROXYETHYL) METHANESULPHONANILIDE HYDROCHLORIDE] (MJ-1999) ON PULMONARY CIRCULATION*

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While the pharmacological actions of adrenergic beta receptor blocking agents specially those pertaining to cardiovascular system have been investigated in detail, there are only scattered reports dealing with their pulmonary vascular effects. Propranolol was shown to exert a variable effect on pulmonary arterial pressure and pulmonary vascular resistance (18). [4-(2-isopropylamino-1-hydroxyethyl) methanesulphonanilide hydrochloride] (MJ-1999) was found to cause an increase in the calculated pulmonary vascular resistance (4). However, the direct effects of these drugs on the lung vessels independent of adrenergic beta receptor blockade have not been elucidated. Hence it was of interest to study their pulmonary vascular effects. Since cardiac and systemic vascular changes are known to modify the pulmonary vascular effects of drugs (2), the actions of propranolol and MJ-1999 on other circulatory parameters and their ability to alter the cardiopulmonary responses to adrenaline and isoprenaline were investigated.

MATERIALS AND METHODS

Experiments were conducted on artificially ventilated mongrel dogs of either sex weighing between 15 and 20 kg. Chloralose (80 mg/kg, i.v.) and pentobarbitone sodium (10 mg/kg, i.v.) were used as anaesthetic agents. Heparin sodium (5 mg/kg, i.v.) was routinely used as anticoagulant. Systemic arterial blood pressure was recorded from carotid artery. Left lower lobe of the lung was perfused at constant rate with mixed venous blood derived from the animal's own right atrium by means of a Rotor pump (3). Perfusion pressure was recorded kymographically. Pulmonary arterial blood pressure was recorded by means of a glass cannula inserted in the central end of the lobar artery. Cardiac contractility was recorded by the suspension method of Jackson (11). Cardiac rate was recorded by using electrocardiogram lead II.

Drugs

The following drugs were used: Hydrochloride salts of racemic propranolol and racemic MJ-1999 [4-(2-isopropylamino-1-hydroxyethyl) methanesulphonanilide hydrochloride] in doses of 0.1, 0.5 and 1.0 mg/kg. Adrenaline hydrochloride, 1 µg/kg and isoprenaline sulphate, 1 µg/kg were given before and 10 min after the adrenergic beta receptor blocking agent. The doses refer to the salts. All drugs were dissolved in normal saline and administered intraarterially by injecting into the rubber tubing close to the cannulated

Received on 20.1.1970
pulmonary artery. The volume injected did not exceed 1 ml. As tested in a few experiments, this volume of normal saline was without any circulatory effect.

**RESULTS**

On intraarterial administration of propranolol and MJ-1999, the first change noticeable was in perfusion pressure. Since the corresponding vein was intact, the effects of injection spread immediately to other parts of cardiovascular system. Propranolol and MJ-1999 in doses of 0.1 mg and 0.5 mg/kg were sometimes tried in the same animal. However, the dose of 1.0 mg/kg was invariably tried in a different animal. The results of individual experiments are graphically shown in Fig 1, 2 and 1 of a typical experiment are illustrated in Fig 3.
As tested in a few experiments, the effect of injection of MJ-1999, the first change noticeable was intact, the effects of injection of propranolol and MJ-1999 in individual experiments are illustrated in Fig. 3.

The results of individual experiments are illustrated in Fig. 3.

Pulmonary perfusion pressure

The control perfusion pressure varied between 25 and 34 mm Hg. Propranolol in 17 experiments and MJ-1999 in 14 experiments decreased the pressure by 3.4 to 22.7% and 3.0 to 42.0% respectively. No change was produced by propranolol in 6 experiments and by MJ-1999 in 2 experiments. In 6 dogs MJ-1999 caused a rise in perfusion pressure of 3.0 to
Typical effects of MJ-1999 and propranolol, (given at the arrow head) on pulmonary arterial pressure (P A P), systemic arterial blood pressure (S A B P) and pulmonary perfusion pressure (P P P).

13.3%. In 2 other dogs, biphasic response was observed: rise (3.0 and 11.8%) followed by fall (6.0 and 11.8%).

Adrenaline caused a rise in perfusion pressure while isoprenaline brought about a fall. After 0.5 mg/kg of propranolol or MJ-1999, the hypertensive effect of adrenaline was augmented in all the experiments and the hypotensive effect of isoprenaline was reduced in
most of the experiments. However, in 2 dogs pretreated with propranolol, the hypotensive effect of isoprenaline was reversed to a hypertensive effect while in 3 other animals (two with MJ-1999 and one with propranolol), it was not appreciably changed.

**Pulmonary arterial blood pressure**

The control pulmonary arterial pressure in the intact lobe ranged from 20 to 25 cm of water. Propranolol in 7 experiments (10 instances) and MJ-1999 in 5 experiments (6 instances) decreased it by 3.7 to 57.1% and 1.0 to 16.0% respectively. In 3 experiments, (two with MJ-1999 and one with propranolol) biphasic effect was exerted : rise ((1.1 to 6.1%) followed by fall (8.6 to 15.0%). In another dog treated with MJ-1999 only rise in perfusion pressure of 5.7% was observed.

Both adrenaline and isoprenaline caused a rise in pulmonary arterial blood pressure in all the dogs. Pretreatment with 0.5 mg/kg of propranolol or MJ-1999, resulted in a reduction of hypertensive effect in all the experiments.

**Systemic arterial blood pressure**

The control systemic arterial pressure ranged from 120 to 180 mm Hg. Propranolol decreased it by 3.0 to 35.6% in 14 experiments (19 instances). MJ-1999 caused a biphasic effect in 13 experiments (17 instances): rise (2.0 to 36.4%) followed by fall (1.3 to 43.6), and purely hypotensive effect (3.2 to 12.8%) in 7 experiments.

Adrenaline caused a rise of blood pressure in 4 experiments and biphasic effect (rise followed by fall) in 3 other experiments. After 0.5 mg/kg of propranolol or MJ-1999, the hypotensive effect of adrenaline was abolished and its hypertensive effect was increased except in one dog. Isoprenaline exerted a fall of systemic arterial blood pressure in 4 dogs. In 3 other experiments biphasic effect was exerted: rise followed by fall. Pre-treatment with 0.5 mg/kg of propranolol or MJ-1999 resulted in blockade of hypotensive and enhancement of hypertensive component of action of isoprenaline in 3 dogs. Further, the hypotensive effect of isoprenaline was reversed to hypertensive effect in 4 experiments.

**Cardiac contractility and rate**

The control heart rate varied between 165 and 225 per min. Propranolol and MJ-1999 exerted negative inotropic and negative chronotropic effects in all except 3 experiments wherein MJ-1999 did not alter the heart rate. The decrease in heart rate ranged between 2.6 and 22.2% with propranolol and between 5.0 and 27.0% with MJ-1999; and decrease in cardiac contractility ranged between 5.7 and 79.0% with propranolol and between 3.4 and 44.4% with MJ-1999.

Both adrenaline and isoprenaline caused increase in heart rate and cardiac contractility in all the experiments. After 0.5 mg/kg of propranolol, the positive chronotropic effect of adrenaline was completely blocked and that of isoprenaline was markedly reduced. Likewise,
positive inotropic effects of adrenaline and isoprenaline were considerably decreased. On pre-
treatment with 0.5 mg/kg of MJ-1999, the positive inotropic and positive chronotropic effects of
adrenaline and isoprenaline were markedly reduced.

**DISCUSSION**

The cardiac (negative inotropic and chronotropic) and systemic hypotensive effects of pro-
pranolol and MJ-1999 are chiefly due to cardiac beta receptor blockade as shown by previous
workers (6, 12, 16, 17, 19). However, the pulmonary vascular effects of these drugs are not
merely the outcome of beta receptor antagonism and are discussed in the light of observations
made by other workers.

Influence of changes in the cardiac output, which is the commonest factor known to
alter the pulmonary arterial pressure (9, 15), was eliminated in the present study by perfusing
one lobe of the lung at constant rate by means of a pump. In these experiments, propranolol
lowered perfusion pressure indicating local pulmonary vasodilator action. Similarly, vasodi-
lation occurred following the administration of MJ-1999. However, in a few instances, the
latter drug caused rise of perfusion pressure indicating pulmonary vasoconstriction.

Existence of adrenergic beta receptors in the lung vessels has been shown by previous workers
(5, 10, 13) and is demonstrable in the present study by the ability of isoprenaline to produce a
decrease in perfusion pressure. Adrenergic beta receptor blockade by MJ-1999 may result in
pulmonary vasoconstriction from the unopposed activity of alpha receptors (4). This raises the
question as to why propranolol, another beta receptor blocking drug, does not share the
property of MJ-1999 in causing pulmonary vasoconstriction. The answer may be sought in the
previous observation that MJ-1999 exhibits intrinsic sympathomimetic activity (1) which
propranolol lacks (6, 7, 8). As expected, beta receptor blockade antagonized the fall in per-
fusion pressure produced by isoprenaline and enhanced the pressor response to adrenaline.

In the intact lobe, propranolol invariably and MJ-1999 predominantly caused a fall in
pulmonary arterial blood pressure which was attributable to direct pulmonary vasodilatation
and decrease in cardiac output as reported previously (14). No attempt was made to elucidate
any temporal relationship between changes in the pressure and those in cardiac contractility or
rate. In a few experiments, MJ-1999 produced hypertension which might be due to its vaso-
constrictor action. Both adrenaline and isoprenaline caused a rise of pulmonary arterial
pressure. This was due to an increase in the cardiac output (2) resulting from cardiac beta
receptor stimulation. Pretreatment with beta receptor antagonists reduced or abolished the
hypertensive effect of these amines. These findings further stress the role of cardiac output
in influencing the pulmonary arterial pressure.

**SUMMARY**

(1) Effects of two adrenergic beta receptor blocking agents, propranolol and MJ-1999,
were investigated on cardiovascular system with special reference to pulmonary circulation in
anaesthetized mongrel dogs. Both the drugs caused systemic hypotension and decrease in
cardiac rate and contractility in most of the experiments.
Effect of Beta Blockers on Pulmonary Circulation

Both the drugs caused predominantly a fall of pulmonary arterial pressure in the perfused lobe indicating a pulmonary vasodilator effect. In a few dogs treated with MJ-1999, there was a rise of perfusion pressure which may have been the result of beta receptor blockade allowing alpha receptor activity to predominate and intrinsic sympathomimetic activity of the compound. Further, beta receptor blockade reduced the fall in perfusion pressure produced by isoprenaline and increased the hypertensive effect of adrenaline.

Pulmonary arterial pressure of the intact lobe was depressed by these drugs in most of the experiments. This could be due to local pulmonary vasoconstriction and decrease in cardiac output. Pulmonary hypertension observed in a few experiments with MJ-1999 was attributable to vasoconstriction. Adrenaline and isoprenaline consistently elicited a pulmonary vasopressor response. Since cardiac beta receptor blockade antagonized this hypertensive effect, the role of cardiac output in influencing the pulmonary arterial pressure is reiterated.

ACKNOWLEDGMENTS

We are thankful to Indian Council of Medical Research, New Delhi for financial assistance. Propranolol hydrochloride was supplied by Imperial Chemical Industries, England and MJ-1999 by Mead Johnson Research Centre, Evansville, Indiana, U.S.A. These generous gifts are acknowledged with gratitude. Technical assistance of Shri M.L. Ramawat is acknowledged with thanks.

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