EFFECT OF IMIPRAMINE ON ADRENERGIC RESPONSES

A. A. SHAIKH*, O. D. GULATI AND H. M. PARIKH**

Pharmacological Research Unit, Council of Scientific and Industrial Research and the Department of Pharmacology, Medical College, Baroda

Summary: In anaesthetised dogs imipramine (IMI) potentiated pressor responses to noradrenaline (NA) and depressor responses to isoprenaline (I) and blocked pressor responses to adrenaline (A), phenylephrine (P) and bilaterol occlusion of common carotid arteries. Higher doses of IMI also blocked the depressor response to I. In animals treated with dichloroisoprenaline, IMI did not block pressor responses to A. In cocainized animals, IMI reduced pressor responses both to A and NA. Potentiation of pressor responses to NA by IMI was somewhat reduced by bilateral vagotomy. In cocainized and vagotomized dogs, the potentiated pressor responses to A were reduced by IMI but those to NA remained unaltered. IMI caused dose-related inhibition of the constrictor effects of I and NA on the rabbit isolated perfused ear preparation. On the rabbit isolated splenic strip preparation, IMI blocked contractile responses to NA noncompetitively. The positive inotropic effects of A, NA and I on the isolated rabbit hearts were potentiated by lower doses of IMI but not by a high dose. It is concluded that in smaller doses IMI has alpha-adrenoceptor blocking and beta-adrenoceptor sensitizing actions and that in higher doses it blocks both receptors. The block of uptake of NA and of compensatory reflexes by IMI accounts for the potentiation of pressor responses to NA.

Key words: imipramine catecholamines alpha-and beta-adrenoceptors compensatory reflexes potentiation block

INTRODUCTION

Imipramine (IMI) enhances the pressor responses to noradranaline (NA) in cat (18) and dog (13, 17). The drug reduces the action of adrenaline (A) on the systemic blood pressure (6, 17). Thoenen *et al.* (21) studying the effect of IMI on responses of spleen to nerve stimulation observed that at higher concentrations it produced an alpha-adrenoceptor blocking effect. Eble (6) reported that IMI reduced the action of A on the perfused leg of dog and had an inconsistent influence on the action of NA. Responses of the nictitating membrane of cat to NA are potentiated more than those to A by IMI (19).

Several explanations for the paradoxical property of IMI in selectively potentiating the pressor responses to NA have been proposed. IMI decreases the uptake of H^3-NA by tissue (2). Prevention of uptake of NA into nerve endings leading to an increase in the levels of circulating NA has been proposed and amply confirmed to be responsible for potentiation (6, 9, 21). Eble (6) attributed the potentiating effect of IMI on NA-induced responses in perfused leg of dog to an inhibition of homeostatic reflex mechanism in addition to an increase in the levels of circulating NA.

Present address: *Sarabhai Chemicals, Baroda. **Alembic Chemical Works, Baroda.

However, these propositions do not provide a satisfactory explanation for the underlying mechanism responsible for the paradoxical property of IMI in selectively blocking the pressor effect of A.

Investigations designed to throw further light on the mechanism of potentiation of responses to NA and inhibition of responses to A by IMI, therefore, seemed to be in order. The present study was undertaken for this purpose.

MATERIALS AND METHODS

Dog blood pressure: Healthy mongrel dogs of either sex weighing 10-20 *kg* were used. The animals were anaesthetized by the intravenous administration of 30 *mg/kg* of pentobarbitone sodium dissolved in normal saline. Anaesthesia was maintained with 3 *mg/kg* of intravenous injection of pentobarbitone sodium as needed. Arterial blood pressure was recorded on a smoked drum from a cannulated left femoral or common carotid artery connected to a U-tube mercury manometer. Injections were made through a prolyethylene cannula inserted into the right femoral vein. Drugs were injected in a volume ranging from 0.1-0.6 *ml* and were washed in with 2 *ml* of 0.9% NaCl solution.

Vagotomy was performed under artificial ventilation. Both vagi were exposed in the neck and severed one by one at an interval of 15 min. A rest period of 30 min was given after bilateral vagotomy.

Isolated perfused rabbit ear: Ears were obtained from young rabbits of either sex weighing 2-2.5 *kg* and perfused as described by Burn (4). A small polyethylene cannula was tied in the central artery of the ear and was connected to Langendorff perfusion assembly. The preparation was perfused with oxygenated Locke heart solution at a temperature of 31 ± 0.5^{0}C and perfusion pressure of 30 *mm Hg*. This pressure was chosen because it gave the most consistent results and did not produce overdistension of the blood vessels. A Stathem pressure transducer (Model-P-23 AA) was connected to Sanborn Twin Viso Recorder (Model 60-1300) to record changes in perfusion pressure. Drugs were injected in a constant volume of 0.5 *ml* in the rubber tubing close to the cannula.

Rabbit splenic strip: Splenic strips 3 *cm* long and 5 *mm* wide were obtained from young rabbits of either sex weighing 1.5-2 *kg* and set up according to the method described by Innes (11) for the preparation of isolated strips of cat's spleen. The strip was suspended in an organ bath containing 40 *ml* of Tyrode solution maintained at 37 C ± 0.5 C and bubbled with air. Isotonic contractions at 0.5 *g* tension were recorded on a smoked drum at 8 times amplification.

Rabbit Heart: Hearts were obtained from rabbits of either sex weighing 1.5-2 *kg* and perfused by the method of Langendorff with oxygenated Locke heart solution. The perfusion pressure was 30 *mm Hg*. The temperature of the perfusion solution was maintained at 29°C. The contractions of the heart were recorded on a smoked drum by means of a Starling heart lever. The

preparation was allowed to stabilise for 30 min before giving drugs. The drugs were injected in the rubber tubing close to the cannula in a constant volume of 0.5 *ml.* The effect of each drugs was studied for 1 min at intervals of 10 min.

Drugs:

The following drugs were used:- (-) adrenaline (A),(-) -noradrenaline bitartrate (NA), isoprenaline sulphate (I), phenylephrine hydrochloride (P), imipramine hydrochloride (IMI), cocaine hydrochloride (COC), angiotensin (ANG) and dichloroisoprenaline hydrochloride (DCI). Doses of all drugs except those of adrenaline and angiotensin are in terms of the respective salt.

RESULTS

Dog blood pressure:

Effect of IMI on responses to A, NA, I, ANG and P: Pressor responses to intravenous injections of fixed doses of NA and P and depressor responses to I were elicited at intervals of 10 min. When A (4 μg or 10 μg/*mg*) was given at intervals of 10 min an initial pressor response followed by a depressor response was elicited. The responses to NA, P and A were reproducible (n=8). ANG injected at intervals of 20 min elicited reproducible pressor responses (n=3).

IMI (1 *mg* or 5 *mg/kg*) reduced the pressor component and enhanced the depressor component of the blood pressure response to A (Fig. 1). The pressor response to NA (4 μg/kg) was 28±7.14% more than that obtained in control animals (Table I). IMI caused dose-related inhibition of the pressor response to P (Fig. 2). The depressor response to I was potentiated by small dose, but

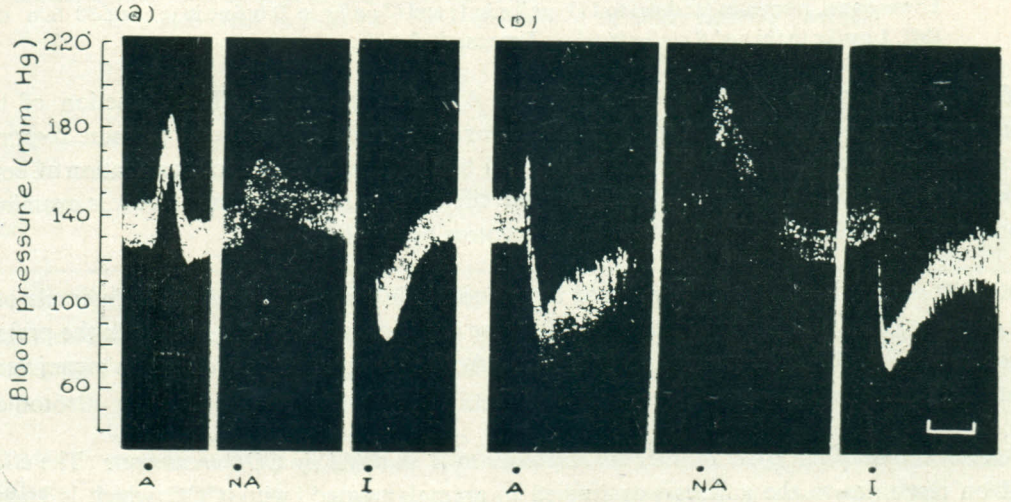

Fig. 1: Dog (12 *kg*), pentobarbitone anaesthesia. Record of carotid arterial blood pressure. Responses to A (4 $\mu g/kg$), to NA (4 $\mu g/kg$) and to I (2 $\mu g/kg$) alone in (a) and 30 min after IMI (5 *mg/kg*) in (b). Time mark, 2 min.

reduced by a large dose of IMI (Fig. 2). ANG (0.1 *μg/kg*)-induced pressor responses were potentiated (41.9±14.1%) by IMI (5 *mg/kg*).

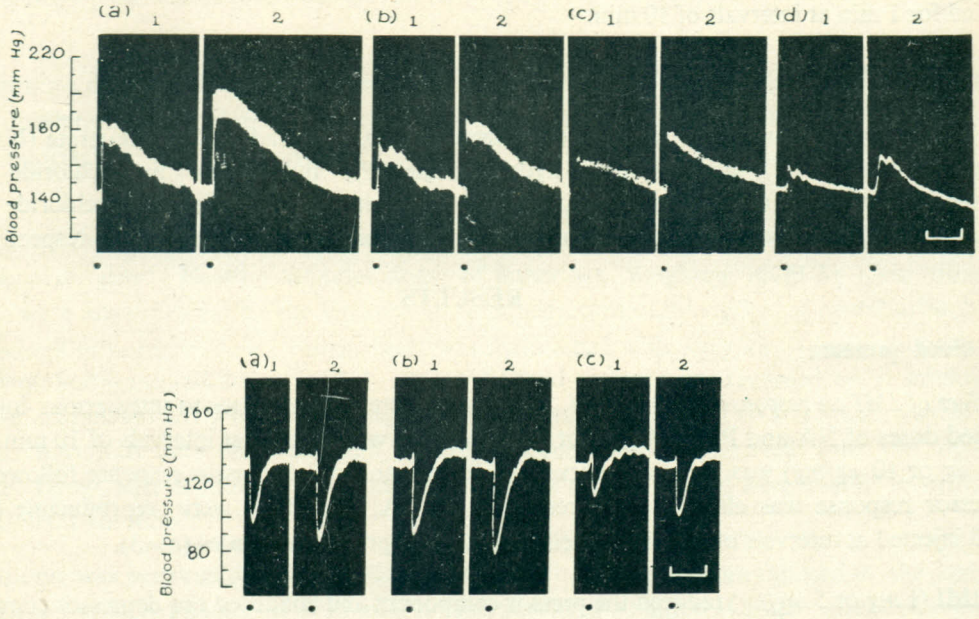

Fig. 2: Dogs (11 *kg* and 10.8 *kg* in upper and lower panels respectively), pentobarbitone anaesthesia. Records of femoral arterial blood pressure. Upper panel, responses (at dots) to P (5 *μg/kg* in 1) and (10 *μg/kg* in 2) before in (a) and 30 min. after IMI, 1 *mg/kg* in (b), 4 *mg/kg* in (c) and 8 *mg/kg* (d). Lower panel, responses (at dots) to I (1 *μg/kg* in 1) and (2 *μg/kg* in 2) before in (a) and 30 min after IMI, 1 *mg/kg* in (b) and 8 *mg/kg* in (c). Time mark, 2 min.

Modification of the effect of IMI on responses to A by DCI treatment: The reduction of the pressor component and enhancement of the depressor component of the blood pressure response to A and enhancement of the depressor response to I by IMI could be due to sensitization of beta-adrenoceptors by IMI. To test this possibility the effect of IMI on response to A was examined after producing complete blockade of beta-adrenoceptors by DCI.

DCI (10 *mg/kg*; n=6) was administered intravenously in three divided doses at intervals of 5 min. I (2 *μg/kg*) now had no depressor effect. In these experiments IMI did not block the pressor response to A (Fig. 3). The pressor response to NA was potentiated as well as in experiments without DCI (Table I).

Modification of the effect of IMI on responses to A and NA by COC treatment: The effect of IMI on responses to the amines was studied in animals treated with COC which is known to block the tissue uptake of NA (15). COC (5 *mg/kg;* n=6) was administered slowly intravenously over a period of 10 to 20 min followed by an intravenous drip at a rate of 2.5 *mg/hr* throughout

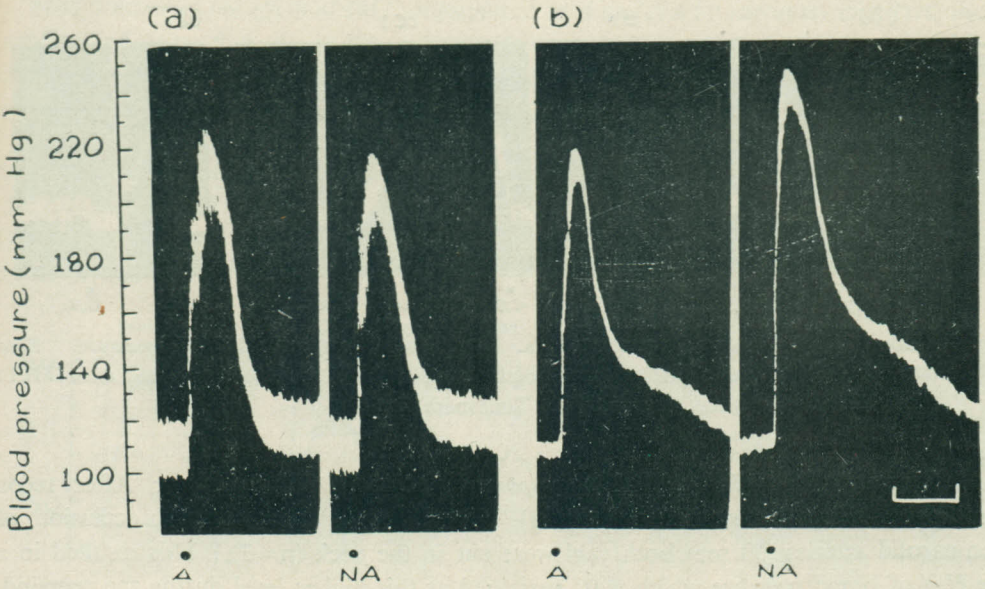

Fig. 3: Dog (11.5 *kg*), pentobarbitone anaesthesia (the dog was treated with DCI, 10 *mg/kg*). Record of femoral arterial blood pressure. Responses to A (4 μg/*kg*) and to NA (4 μg/*kg*) alone in (a) and 30 min after IMI (5 *mg/kg*) in (b). Time mark, 2 min.

TABLE I: Modification of the effect of IMI on the blood pressure responses of anaesthetised dogs to NA and A by some procedures.

	Mean percentage increase (+) or decrease (—) in blood pressure ±S.E.M.					
	IMI	*DCI & IMI*	*COC*	*COC & IMI*	*Vagotomy*	*Vagotomy & IMI*
NA (4μg/*kg*)	+28±7.1 (8)	+27.3±4.3 (6)	+30.7±5.6 (6)	+16.9±3.8 (6)	+6.3±1.2 (3)	+21.3±3.8 (3)
A (4 μg/*kg*)			+9.4±3.5 (6)	—9.3±3.9 (6)	+6.3±1.2 (3)	—6.9±1.9 (3)

Figures in parentheses indicate the number of observations.

the experiments. Pressor responses to A (4 μg/*kg*) and NA (4 μg/*kg*) were potentiated by 9.4±3.5% and 30.7±5.6% respectively (Table I). In these experiments IMI (5 *mg/kg*) reduced pressor responses to A and NA (Table I).

Modification by IMI of the effect of bilateral carotid occlusion: Occlusion of the common carotid arteries at intervals of 10 min for a period of 30 sec elicited pressor responses. When 3 to 4 responses elicited in this manner were constant, IMI was given. There was a dose related potentiation of the pressor responses to NA and inhibition of the pressor responses to bilateral occlusion of the common carotid arteries (Fig. 4; n=3).

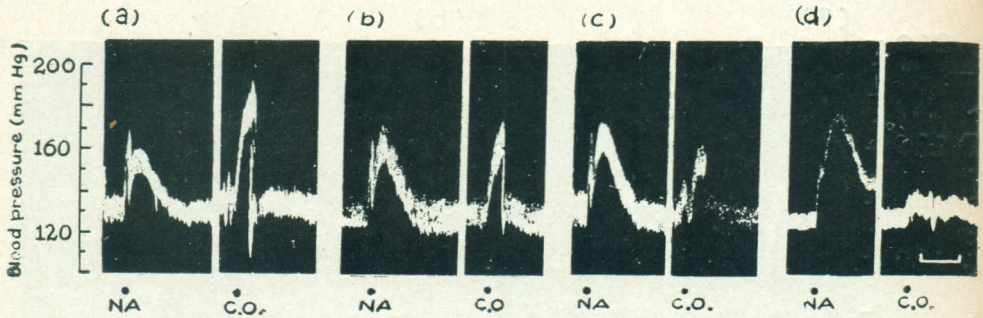

Fig. 4: Dog (14 *kg*), pentobarbitone anaesthesia. Record of femoral arterial blood pressure. Responses to NA (4 μg/*kg*) and to bilateral carotid occlusion (30 sec. at C.O) before in (a) and after IMI 1 *mg/kg* in (b), 2 *mg/kg* in (c) and 8 *mg/kg* in (d). Time mark, 2 min.

Modification of the effect of IMI on responses to A and NA by vagotomy: After recording a control panel of responses to A (4 μg/*kg*), NA (4 μg/*kg*) and bilateral occlusion of the common carotid arteries (30 sec), both vagi were cut in the neck (n=3). This resulted in a rise (30 *mm Hg*) of blood pressure which was sustained at this higher level during the remainder of the experiment. Thirty min after bilateral vatotomy, pressor reponses to A and NA were equally potentiated (6.3±1.2%) but those to bilateral occlusion of the common carotid arteries were reduced. Thirty min after the administration of IMI (5 *mg/kg*) pressor responses to A were reduced but those to NA were potentiated (Table I).

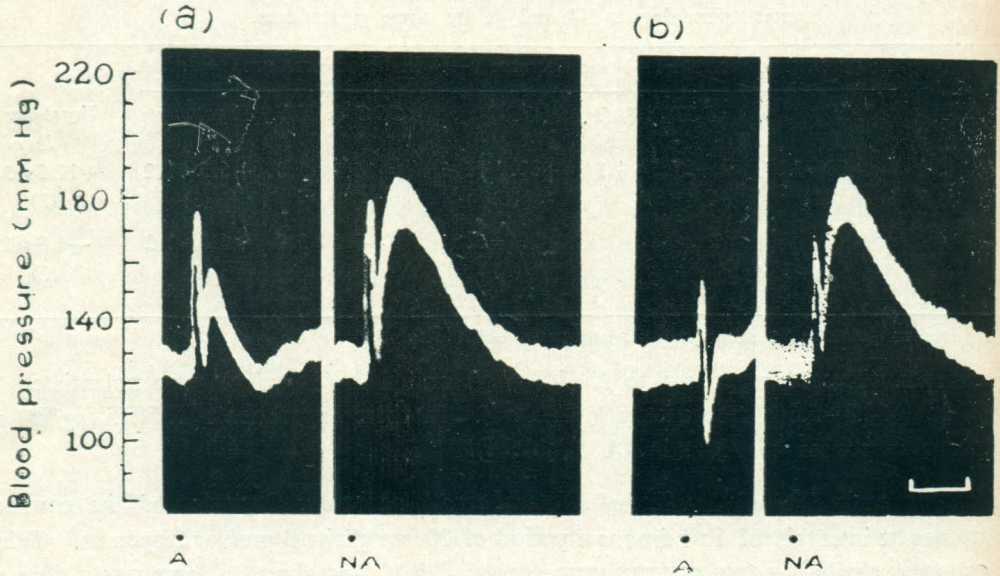

Fig. 5: Dog. (10.5 *kg*), pentobarbitone anaesthesia (the dog was vagotomized and given cocaine, 10 *mg/kg* followed by infusion, 2.5 *mg/hr*). Record of femoral arterial blood pressure. Responses to A (4 μg/*kg*) and to NA (2 μg/*kg*) alone in (a) and 30 min. after IMI (5 *mg/kg*) in (b). Time mark, 2 min.

Modification of the effect of IMI on responses to A and NA by vagotomy and COC treatment: In vagotomized dogs, 5 *mg/kg* of COC followed by an infusion at the rate of 2.5 *mg/hr* was given (n=3). Thirty min later responses to A and NA were potentiated. IMI was now given. Thirty min later, pressor responses to A were reduced and those to NA were unaffected (Fig 5).

Isolated perfused rabbit ear preparation: Vasoconstrictor responses to A (5×10^{-8}, 1×10^{-7}, 1×10^{-7} and 2×10^{-7} *g*) and NA (8×10^{-8}, 1.5×10^{-7} and 2×10^{-7} *g*) were determined in duplicate at intervals of 10 min (n=6). IMI caused a dose-related inhibition of the constrictor effects of A and NA (Fig. 6).

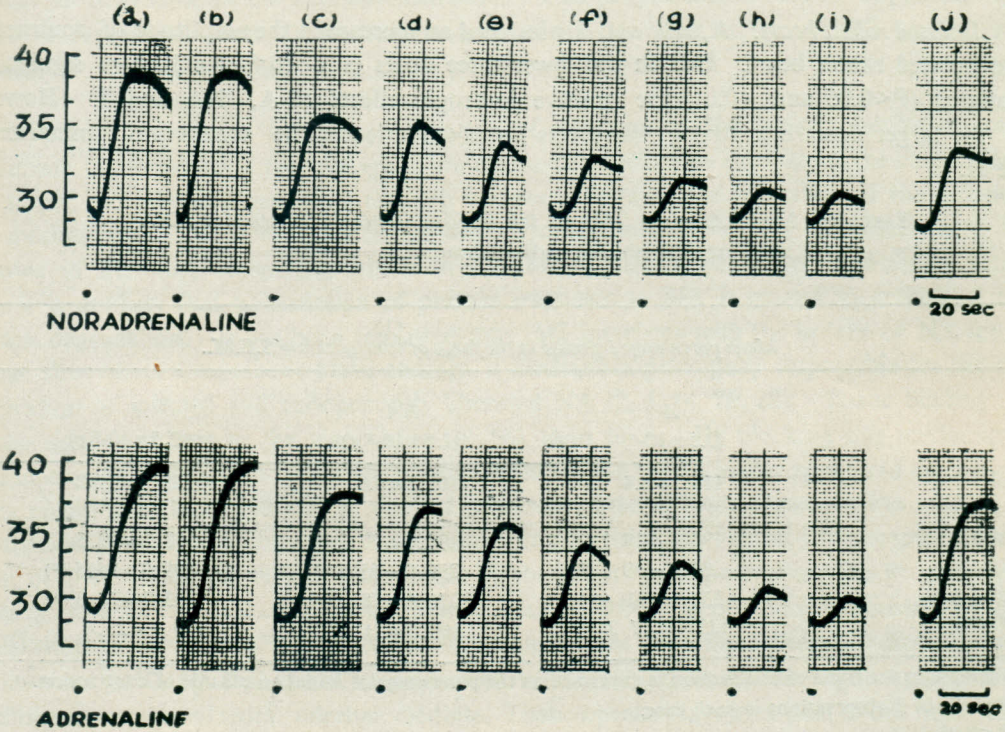

Fig. 6: Isolated perfused rabbit ear preparations: Record of perfusion pressure (*Hg mm*). Responses (at dots) to NA (2×10^{-7} *g*) in the upper panel and to A (2×10^{-7} *g*) in the lower panel before (under a, b and j) and 5 min after IMI 5×10^{-6} *g* (under c), 1×10^{-5} *g* (under d), 2×10^{-5} *g* (under e), 4×10^{-5} *g* (under f), 8×10^{-5} *g* (under *g*), 1.6×10^{-4} *g* (under *h*) and 3.2×10^{-4} *g* (under i). Time mark, 20 sec.

Rabbit splenic strip preparation: Cumulative dose-response curves for NA (1.25×10^{-7} to 1×10^{-6} *g*) were obtained by the administration of increasing concentrations of the amines allowing the contraction to develop fully after each administration (4 min). When two successive dose-response curves elicited at intervals of 45 min were alike, the preparation was exposed to IMI (2×10^{-7}, 4×10^{-7}, 8×10^{-7}, 1.6×10^{-6} and 3.2×10^{-6} *g;* n=3 for each

dose) for 10 min before the addition of NA. IMI produced a dose-related inhibition of the responses to NA. Although it was possible to obtain maximum responses to NA in the presence of IMI, the shift to the right of the dose-response curve was not parallel. The data were therefore subjected to analysis according to the method of Arunlakshna and Schild (1). According to this method, log (dose- ratio -1) was plotted on the ordinate and -log M of IMI was plotted on the abscissa (pAx plots). Dose ratios were obtained as the ratios of equiactive doses of NA in the presence and absence of IMI (8). The slope (b) of the regression line of pA_x plot was —1.9. This values is much higher than the theoretical value of slope of -1 for competitive antagonism. Thus IMI acted noncompetitively.

Isolated rabbit heart: A, NA and I produced an increase in the amplitude of contractions of the isolated rabbit heart. IMI in the lower three doses ($1 \times 10^{-6} - 4 \times 10^{-6}$ *g*) significantly potentiated ($P<0.05$ and <0.01) the positive inotropic effects of A, NA and I. However, with the larger dose (8×10^{-6} *g*) there was no potentiation. The results are summarized in Table II.

TABLE II: Modification by IMI of the positive inotropic effects of A, NA and I in rabbit isolated perfused hearts.

	(1) *Mean percentage increase in the force of contraction ± S.E.M.*.		(2)
	A (2.5 x 10-⁶)	*NA* (2.5 x 10-⁶ *g*)	*I* (2.5 x 10-⁶ *g*)
Control	114.2 ± 8.4	109.5 ± 6.0	129.3 ± 16.2
After IMI			
1x10-⁶ *g*	199.4 ± 18.2 (3)	191.1 ± 27.3 (3)	358.2 ± 89.5
2x10-⁶ *g*	281.4 ± 39.5 (3)	290.0 ± 51.8 (3)	409.3 ± 95.5 (3)
4x10-⁶ *g*	237.4 ± 21.4 (4)	276.9 ± 28.2 (4)	383.7 ± 74.6 (3)
8x 10-⁶ *g*	121.4 ± 17.3	160.5 ± 21.3	199.9 ± 23.4

(1) Increase in the force of contraction is expressed as the percentage of initial amplitude of contraction.
(2) Results of 3 observations in each case.
(3) $P<0.05$
(4) $P<0.01$

DISCUSSION

Selective blockade of the pressor responses to A and potentiation of those to NA following IMI have been demonstrated and various explanations have been offered to account for this paradoxical phenomenon. Theonen *et al.* (21) reported that higher concentrations of IMI exhibit an adrenergic blocking effect in addition to its inhibiting effect on rapid inactivation of NA. It appears that an exact pharmacological characterization of IMI as an adrenergia

blocking agent has been made difficult by the ability of the drug to potentiate the pressor effect of NA in doses which greatly reduce the pressor effect of A.

NA which acts predominantly on the alpha-adrenoceptors alicits a pressor response under all circumstances whereas the direction and magnitude of the blood pressure change following A depends on the relative prominence of its vasoconstrictor and vasodilator effects. In the present study IMI in smaller doses was found to potentiate the vasodilator component of action of A, the depressor effect of I and the positive inotropic effects of A, NA and I on the isolated rabbit heart. Thus IMI in smaller doses appears to potentiate catecholamine responses mediated through an activation of the beta-adrenoceptors. This proposition is further supported by the results of experiments with DCI where reversal of the blocking action of IMI on the pressor response to A was obtained.

Factors responsible for the potentiation of responses to NA include inhibition of the mechanism (s) terminating the biological life of the catecholamine (uptake of the catecholamine into stores; metabolic degradation through various pathways) and inhibition of the compensatory mechanisms. IMI does not interfere with monoamine oxidase (16). Similarly there is no evidence in literature suggesting inhibition by IMI of catechol-o-methyl transferase activity. Thus it is unlikely that potentiation of pressor responses to NA is caused by inhibition of its enzymic degradation. It has been suggested that IMI interferes with the uptake of NA into the storage sites of its sympathetic nerve endings, a mechanism principally responsible for the rapid inactivation of injected and endogenously liberated NA (2, 5, 14, 20, 22). Tissue binding plays a more significant part in the inactivation of NA than of A. By blocking this mechanism of rapid inactivation of NA the effective concentrations of NA reach higher peaks and decline more slowly resulting in increased and prolonged responses of the effector organ. In the case of NA, potentiation caused by inhibition of the uptake apears to mask the alpha-adrenoceptor blocking action of IMI. This suggestion is supported by the results of experiments with P and ANG. Feldberg and Lewis (7) have reported that as little as 0.001 μg of ANG administred by close-arterial route in cats caused release of catecholaminse from the adrenal medulla. Potentiation of responses to ANG by IMI could be attributed to the inhibition of the tissue uptake of the catecholamines released from adrenal medulla. Tissue uptake plays little part in the inactivation of P (12) and responses to P were blocked by IMI. Results of experiments in animals in which tissue uptake of NA was blocked by treatment with COC demonstrated that no further potentiation of pressor response to NA was possible. On the contrary, pressor response by NA was now reduced following IMI.

Compensatory reflexes through the pressure sensitive caroticoaortic baroreceptor system and increased reflex vagal tone play a significant role in the termination of the pressor responses to catecholamines. Potentiation of the pressor effect of NA after IMI could thus be due to an inhibition of these compensatory reflexes. That this might have party contributed to potentiation is suggested by the fact that potentiation was less in vagotomized animals than in control

animals (Table I). Inhibition of pressor response to bilateral common carotid artery occlusion by IMI further supports this contention.

In the present study IMI has been shown to block alpha-adrerocetor mediated responses in rabbit ear vasculature, rabbit splenic strip and dog blood pressure. The adrenergic blocking action of IMI on vascular smooth muscle of isolated rabbit ear indicates that the uptake of NA into the storage sites in blood vessels, as suggested by Berkowitz *et al.* (3) is of minor importance. Antagonism by IMI of the responses to NA in splenic strips was noncompetitive since although maximum responses to NA could be obtained, the shift to the right the dose-response curve was nonparallel and the slope value of the regression line of pA_x plot was considerably higher than the theoretical value of -1 for competitive antagonism (1). Hrdina and Ling (10) demonstrated a noncompetitive antagonism for desmethylimipramine against NA on the isolated perfused renal artery of the rat.

It is concluded that IMI (i) in smaller doses potentiates those responses to catecholamines which are mediated through an activation of the beta-adrenoceptor and blocks those responses which are mediated through an activation of alpha-adrenoceptor, (ii) potentiates pressor responses to NA by inhibiting its uptake into sympathetically innervated tissues and by blocking compensatory reflex mechanisms and (iii) in higher doses exhibits an adrenoceptor blocking action (both alpha and beta).

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