SOME CARDIOVASCULAR ACTIONS OF IPRONIAZID AND PYROGALLOL

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Recent advances in pharmacology have made available useful enzyme inhibitors. Iproniazid blocks the action of monoamine oxidase (17), and pyrogallol is a catechol O-mothyl transferase inhibitor (3) (2). With the availability of these inhibitors it has become possible to probe into the finer details of the activity of catecholamines, and sympathetic nervous system. The present work has been undertaken to study the effect of these inhibitors, on the heart and blood pressure.

MATERIAL AND METHODS

Effects of various doses of iproniazid, and pyrogallol were seen on isolated and intact heart preparations. Perfused rabbit heart, isolated rabbit auricle and frog heart perfusion were set up by the methods as described by Burn (5). Straub heart preparation was set up as described by Gaddum (9). Auricular and Ventricular contractions were recorded in dog by the suspension method of Jackson (10).

Effects of iproniazid and pyrogallol on blood pressure were studied on mongrel dogs weighing between 8 to 15 kg. Anaesthesia used was pentobarbitone 30 mg/kg intravenously. E. C. G. was taken on conventional bipolar lead II employing inkwriting oscillograph.

The manner in which iproniazid and pyrogallol modified the effects of carotid occlusion, central vagal stimulation, epinephrine and norepinephrine, on blood pressure were observed in bilaterally vagotamized dogs. After taking control responses with various procedures and drugs, iproniazid or pyrogallol was injected in dose of 100 mg/kg. One hour after the injection of iproniazid and 20 minutes after the injection of pyrogallol the procedures and drugs were repeated. A procedure was adopted or the drug was injected 10 minutes after the effect of previous procedure or drugs had passed off. Central Vagal Stimulation was done by stimulating both the vagi with bipolar electrodes. 10 Volt intensity square wave pulses of 5 millisecond duration were given at a frequency of 30 per second for an accurately timed 10 second interval. Maximum change during the 10 second period or few seconds thereafter was considered. Bilateral carotid occlusion was done for 30 seconds. In addition epinephrine 5 mcg/kg ; and norepinephrine 5 mcg/kg were injected.

OBSERVATIONS

Rabbit Heart Perfusion :

Iproniazid in doses of 0.1, 0.5 and 1 mg had no effect on the heart rate or amplitude. Coronary flow was slightly increased for 1 min. with 0.5 and 1 mg dose. In 3 mg dose there was very slight reduction in the heart rate but a significant increase in

TABLE I

Effect of iproniazid and pyrogallol on rabbit heart perfusion.

Drug	Dose in mg	No. of obser vation	Rate/min. Initial	Rate/min. Change	Rate/min. Duration in min.	Amplitude in mm Initial	Amplitude in mm Change	Amplitude in mm Duration in min.	Coronary Flow ml/min Initial	Coronary Flow ml/min Change	Coronary Flow ml/min Duration. in min
Iproniazid	0.1	5	89 (82-96)	—	—	57 (50-76)	—	—	7.8 (6.4-9.2)	—	—
	0.5	5	89 (82-96)	—	—	57 (50-76)	—	—	7.8 (6.4-9.2)	—	—
	1.0	5	89 (82-96)	—	—	57 (50-76)	—	—	7.8 (6.4-9.2)	—	—
	3.0	5	89 (89-96)	5 (3-7)	2.5 (2-3)	57 (50-76)	8 (7-11)	2.5 (2-3)	7.8 (6.4-9.2)	4.8 (4.4-5.2)	2.5 (2-3)
	5.0	5	89 (82-96)	7 (4-10)	6 (4-7)	57 (50-76)	15 (14-17)	>30	7.8 (6.4-9.2)	6.9 (6.4-7.2)	10 (8-12)
	10.0	1	68								
			Diastolic Arrest. No recovery								
Pyrogallol	0.1	5	75 (62-88)	—	—	65 (57-68)	—	—	8.4 (7.2-9.8)	—	—
	0.5	5	75 (62-88)	—	—	65 (57-68)	—	—	8.4 (7.2-9.1)	—	—
	1.0	5	75 (62-88)	—	—	65 (57-68)	—	—	8.4 (7.2-9.1)	—	—
	5.0	5	75 (62-88)	8 (6-10)	2	65 (57-68)	4 (3-5)	2	8.4 (7.2-9.1)	—	—

coronary flow. The effect lasted for 2-3 minutes. With 5 mg doses the rate was insignificantly altered, the amplitude reduced by about 25% and the coronary flow increased markedly. The effect on coronary flow and heart rate lasted for about 10 minutes, but the amplitude did not return to normal for the 30 minutes period observed.

In one experiment 10 mg dose produced diastolic arrest from which the heart did not recover. The coronary flow showed marked increase and in 5 minutes time returned to normal value. Pyrogallol in 0.1, 0.5 and 1 mg dose had no effect on the rate, amplitude or coronary flow. In 5 mg dose it produced a slight reduction in rate and an insignificant reduction in amplitude lasting for 1-2 minutes but there was no effect on coronary flow.

Isolated Rabbit Auricle :

Iproniazid in 0.1 and 0.3 mg/ml concentration produced 15 and 33% reduction in amplitude without any effect on the rate. The reduction lasted for not more than 1 minute. In concentration of 0.75 mg per ml the drug produced diastolic arrest from which the auricle recovered within two minutes of washing. With 0.1 and 0.5 mg/ml concentration of pyrogallol there was no effect on the rate or amplitude of contraction. 1 mg/ml concentration produced slight reduction and 2 mg/ml concentration produced 25% reduction in the rate. There was no effect on the amplitude with any of these concentrations.

Frog Heart Perfusion :

Iproniazid in doses of 0.1 and 0.5 mg had no effect on the rate or amplitude which were slightly reduced with 1 mg dose. With 2 mg dose there was about 15% reduction in rate and 25% reduction in the amplitude. The duration of these reductions was 1 minute. In 3 mg dose reduction in rate and amplitude was of the order of 30-60% and 65-70% respectively. The duration of reduction was 2 minutes. In 4 mg doses the drug produced a diastolic arrest from which the heart recovered completely in 2-3 minutes time.

Pyrogallol had no effect in 0.1, 0.5 and 1 mg dose on the frog heart. It reduced slightly the rate and amplitude in 5 mg dose and this reduction was 20-30% with 10 mg. The effect did not last for more than two minutes.

Straub Heart :

Iproniazid in 0.05 mg/ml had no effect but in 0.1 mg/ml produced slight decrease in the rate and amplitude. The 0.5 mg/ml dose produced transitory diastolic arrest followed by beating of the heart with slower rate and a diminished amplitude. The heart recovered within a minute after it was washed. Pyrogallol produced 25% reduction in the rate and amplitude with 0.05 mg/ml concentration. This reduction was about 50% in 0.1 mg/ml concentration, and with 0.5 mg/ml concentration there was transitory diastolic arrest followed by a very slowly beating heart. The force of contraction was also reduced. The heart quickly recovered when it was washed free of drug.

Heart in Situ :

In doses of 25, 50 and 100 mg/kg neither iproniazid nor pyrogallol produced any significant change in the force of contractions of the auricle or ventricle. There was no

TABLE II

Effects of iproniazid and pyrogallol on the blood pressure and heart rate of dog

Drug	Dose mg/kg	No. of observations	Blood pressure in mm of Hg				Heart Rate/min			
			Before	After	Change	Duration in minutes.	Before	After	Change	Duration in minutes.
Iproniazid	25	5	125 (120-136)	125 (120-136)	—	—	136 (116-144)	136 (116-144)	—	—
	50	5	134 (126-144)	112 (106-122)	-22 (-18to-26)	15	146 (124-170)	166 (138-210)	+20 (14to25)	15
	100	5	116 (116-120)	76 (69-88)	-40 (-38to-49)	45	170 (160-184)	202 (180-216)	+32 (20-46)	45
Pyrogallol	25	5	146 (136-158)	146 (136-158)	—	—	129 (120-141)	129 (120-141)	—	—
	50	5	124 (119-132)	130 (122-140)	6 (3-8)	5	117 (108-125)	117 (108-125)	—	—
	100	5	125 (118-134)	146 (142-156)	+21 (20-22)	10	114 (106-117)	104 (94-110)	10 (9-12)	10

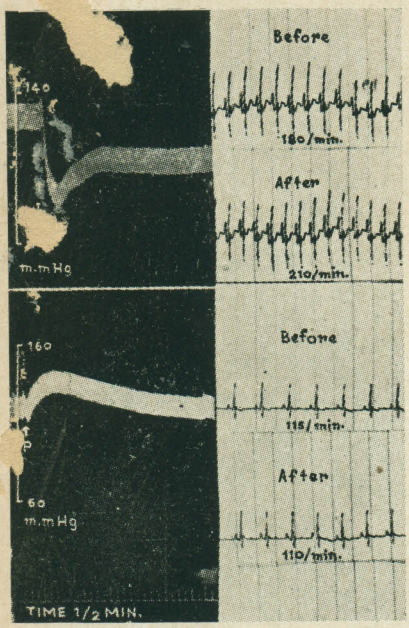

Fig. 1. Effect of drugs on blood pressure and Electrocardiogram. I - iproniazid, P - pyrogallol. The effect shown is of 100 mg/kg I. V. dose of each drug.

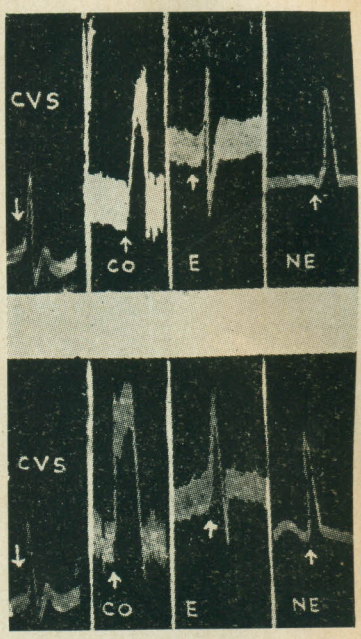

Fig. 2. Effect of various procedures and drugs on the blood pressure of dog before and after injection of Iproniazid (100 mg/kg). CVS - central vagal stimulatioo : Co - carotid occlusian : E - epinephrine NE - norepinephrine. Upper tracings are before and lower tracings are after the injection of iproniazid. The figure shows typical responses. They are taken from different dogs but the tracings of each procedure/drug before and after iproniazid are from the same animal.

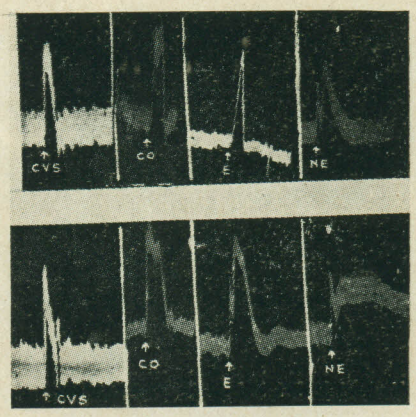

Fig. 3. Effect of various procedures and drugs on the blood pressure of dog before and after injection of pyrogallol (100 mg/kg). CVS - central vagal stimulation : CO - carotid occlusion : E - epinephrine N - norepinephrine. Upper tracings are before and lower tracings are after the injection of pyrogallol. The figure shows typical responses. They are taken from different dogs but the tracings of each procedure/drug before and after pyrogallol are from the same animal.

effect on rate either except with 100 mg/kg iproniazid which produced slight tachycardia. It was secondary to fall in blood pressure and was not seen in bilaterally vagotomized animals.

BLOOD PRESSURE

The effects of the drugs on the blood pressure of dog are shown in Table 2 and Fig. 1. Iproniazid in 25 mg/kg dose had no effect on blood pressure but in doses of 50 and 100 mg/kg it produced a fall of 8 to 26 and 28 to 40 mm of Hg respectively. As is seen in Fig. 2 with iproniazid the blood pressure after partial recovery tends to remain low for a long time and it did not recover even upto 45 minutes. 25 mg/kg dose of pyrogallol had no effect and in dose of 50 mg/kg it produced slight rise in blood pressure (3 to 8 mm of Hg) which returned to normal within 5 minutes. In 100 mg/kg dose pyrogallol produced a rise of 18-22 mm of Hg in blood pressure which returned to normal in less than 10 minutes. There was insignificant slowing of the heart rate.

Iproniazid in 100 mg/kg produced modifications in the blood pressure responses to various procedures which are shown in Table 3 and Fig. 2. There was either no change or only slight decrease in the responses to carotid occlusion, central vagal stimulation, epinephrine and norepinephrine.

The effects of 100 mg/kg pyrogallol on the blood pressure responses to various procedures are shown in Table 3 and Fig. 3. There was increase in responses to carotid

TABLE III

Effects of carotid occlusion, central vagal stimulation and injections of epinephrine, and norepinephrine, on the blood pressure of dog before and after iproniazid and pyrogallol

	No. of observations	Iproniazid 100 mg/kg Blood Pressure response in mm of Hg Mean (Range)		No. of observations	Pyrogallol 100 mg/kg Blood Pressure in mm of Hg Mean (Range)	
		Before drug	After drug		Before drug	After drng
Carotid Occlusion	5	47 (30-64)	44 (24-60)	5	49 (37-60)	57 (44-68)
Central Vagal Stimulation	5	58 (30-85)	56 (28-80)	5	53 (40-73)	62 (43-81)
Epinephrine	5	36 (28-50)	36 (24-45)	5	50 (37-64)	56 (45-70)
Norepinephrine	5	53 (36-74)	52 (32-74)	5	48 (34-71)	57 (38-84)

Mean initial blood pressure before and after drug was 138 mm. with a range of 11.6-156 mm. Hg.

occlusion, central vagal stimulation, epinephrine and norepinephrine. With epinephrine and norepinephrine it was also observed that even if the response did not alter much, the duration definitely increased. The effect seen was more on norepinephrine than on epinephrine response.

DISCUSSION

With iproniazid increased coronary flow and negative inotropic action is seen in isolated heart preparations as also reported in isolated heart by Allmark *et al* (1) and Pletscher and Pellmont (13); and in heart 'in situ' by Zebinden (15). Because of the coronary dilator action the drug was tried for the treatment of angina pectoris with some beneficial effect.

The mechanism of this beneficial effect is a subject of controversy. Zebinden (15) proposed that the antianginal effect may be due to serotonin-induced coronary dilatation. This suggestion is based on the observation that the repeated injection of monoamine oxidase inhibitors increase the blood serotonin level (12) and that serotonin is a known coronary dilator (8). The latter workers however proposed that the beneficial effects of iproniazid in angina could be because of the negative inotropic action of the drugs as seen in isolated heart. This contention seems doubtful as no singificant negative inotropic effect is observed in the intact animal. The effects of pyrogallol on the isolated heart preparations cannot be explained by its Catechol-O-Methyl Transferase inhibition activity. This is because C-OMT concentration in the heart is very low (7), and its inhibition alone is not sufficient to explain these effects, which appear to be independant of its C-OMT inhibitory activity.

Iproniazid produced a sustained fall in blood pressure which was not affected by bilateral vagotomy. This finding is different from that of Leusen (11) who observed no significant fall in animals with intact vagi, but a long lasting fall in bilaterally vagotomized animals.

Pyrogallol in a 100 mg/kg dose raised the blood pressure of dog by 18-22 mm of Hg. It returned to normal within 10 minutes. Such a rise was also seen in animals with both the vagi cut. It appears that this rise is an expression of the prolongation of the action of circulating epinephrine and norepinephrine consequent upon the inhibition of C-OMT.

The effects of carotid occlusion, central vagal stimulation, injection of epinephrine and norepinephrine were unchanged or only slightly decreased by iproniazid and increased after pyrogallol. The absence of potentiation after iproniazid shows that the amine oxidase is not an important enzyme in destruction of epinephrine and norepinephrine. The decrease produced by iproniazid may be because of its greater affinity for the cell receptor sites of blood pressure regulating centres than norepinephrine. Zeller (16) has however postulated an adrenergic blocking effect of proniazid (4). Potentiation due to pyrogallol is because it inhibits O-methyl transferase which is important enzyme in destruction of epinephrine and norepinephrine. With pytrogallol the increase in the pressor effects of epinephrine and norepinephrine may no always be observed, but the duration of action of these amines is always prolonged. The pressor effect of norepinephrine is prolonged more frequently than that of epinephrine. Wylie *et al* (14) explain this difference between epinephrine and norepinephrine pressor

offects after pyrogallol by a higher affinity of norepinephrine for C-OMT.

The observations on iproniazid and pyrogallol bring out an important inference. The former does not have any effect or only an insignificant antagonistic effects on the pressor responses to central vagal stimulation, carotid occlusion, epinephrine and norepinephrine. It shows that amine oxidase dose not have much significant role to play in the metabolism of epinephrine and norepinephrine. The augmentation of responses to central vagal stimulation, carotid occlusion, epinephrine and norepinephrine produced by pyrogallol is also moderate and not as marked as one witnesses with acetylcholine when cholinesterase inhibitors are used. These observations are in line with the view of Crout (6) that the physiologic inactivation of circulating norepinephrine at the receptor sites probably does not require metabolic destruction of the amine by these enzymes.

SUMMARY

Effect of iproniazid and pyrogallol were studied on the heart and blood pressure. The way in which these drugs modified blood pressure response to carotid occlusion, central vagal stimulation, epinephrine and norepinephrine were also observed. Iproniazid has a negative inotropic and chronotropic and a coronary dilator action on isolated heart preparations. Pyrogallol has only a negative chronotropic action on isolated heart. Iproniazid produces a fall in blood pressure which after partial recovery remains low for more than 40 minutes. Pyrogallol produces a rise of blood pressure of short duration. Responses to central vagal stimulation carotid occlusion, epinephrine and norepinephrine on blood pressure are unaffected or only slightly reduced by iproniazid but are invariably potentiated by pyrogallol.

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