The Adrenergic Blocking Activity of Pure Beta Blockers in Comparison with Labetalol (α and β Blockers)

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This study was carried out in the Laboratory of Experimental Pharmacology Allama Iqbal Medical College.Anaesthetized dogs were used as the experimental animals. Recording of the carotid arterial pressure was taken on a kymograph. Adrenaline and Isoprenaline were given in two doses each (A_1, A_2, I_1, I_2) to get their pressor and depressor responses (Control).Then the animal was injected with the drug under study in a dose of 2.5 mg/kg intraveneously. The same doses A_1, A_2, I_1, I_2 were repeated in presence of the Beta Blocking drug. It was seen that Prophranolol, Timolol and Atenolol (Pure Beta receptor blockers) almost doubled the pressor response to adrenaline; whereas Labetalol (a β and α blocker) allowed only a minimal rise in the blood pressure. As regards depressor activity of Isoprenaline, Labetalol showed a very strong blocking effect, whereas the blockade produced by the Pure Beta Blockers, was about on third of the depressor effect.

Key words: Beta Adrenergic Blocking Agents Pressor Response Catecholamines- Depressor Response

Beta Adrenergic receptor blocking drugs have added a new dimension to the management of cardiovascular disorders. Over the past many years Beta adrenergic receptor blocking drugs have become increasingly popular in the treatment of hypertension, ischaemic heart disease and cardiac dysrhythmias.

Materials and Methods

This study was carried out in the Laboratory of Experimental Pharmacology in Allama Iqbal Medical College.

The department of Pathology Allama Iqbal Medical College supplied the animals used. The Beta Adrenergic Blocking Agents under study were:

Propranolol (Inderal) - Imperial Chemical Industries, U.K.
Atenolol (Tenormin) - Imperial Chemical Industries, U.K.
Timolol (Blocadren) - Merck, Sharp & Dhome, U.S.A.
Labetalol (Trandate) - Glaxo, Pakistan.

Each product was used in the pure powder form and was weighed accurately in an electrical balance.

The modifying effect of the Beta Adrenergic Blocking Agents on the pressor/depressor activity of Adrenaline and Isoprenaline was studied.

Dogs were anaesthetized with intravenuous administration of pentobarbitone sodium 35 mg/kg body weight. They were prepared accordingly for the recording of mean carotid arterial blood pressure and respiration.

When the animal had rested for about half an hour after the surgical manipulation, a few inches of the normal recordings of respiration and blood pressure were taken on the smoked paper of the Kymograph.

Then two doses of Adrenaline A_1 and A_2 and two doses of Isoprenaline I_1 and I_2 were injected intravenously at intervals of 5 minutes each. These doses had been determined by preliminary experiments. It had been found, that Adrenaline 1.25 and 2.5 μg and Isoprenaline 1 and 2 μg gave comparable pressor and depressor responses respectively. These doses were injected at intervals of five minutes each so that the effect of the previous dose passed off before the next injection Fig 1,2. After recording the pressor and depressor effect of Adrenaline and Isoprenaline; Propranolol 2.5 mg/kg was injected intravenously and the same doses of Adrenaline and Isoprenaline were repeated at the same intervals. Their effect on the blood pressure was recorded Fig.3.

The modification produced by Propranolol in the pressor and depressor responses of Adrenaline and Isoprenaline respectively was recorded.

Similar experiments were done with other Beta Adrenergic Blocking Agents. Six different animals were used for each Beta Adrenergic Blocking Agents.

Results

The rise in the blood pressure produced by both the doses A_1, A_2 was seen to be almost doubled in presence of Propranolol. Besides the small fall in the blood pressure, seen immediately after setting down of the rise, due to the prolonged Beta effect of Adrenaline was also seen to be absent.

As the same procedure was repeated in six different experiments with Propranolol, the mean value alongwith standard error was calculated. The "t" value was determined by the "t" test for paired variates.

Similar experiments were done with Timolol, Atenolol and Labetalol (Figure 4, 5, 6) Timolol and Atenolol showed a modification of the pressor responses of Adrenaline almost similar to Propranolol. Six different experiments were done for each of them. Their mean values alongwith standard error have been presented in an abbreviated form in Table 1.

Statistical significance of the modifying effect of Propranolol, Timolol and Atenolol on the pressor response of Adrenaline has been calculated. It has been found that the increase in mean arterial blood pressure produced by

the Beta Adrenergic Blocking Agents with both the doses of adrenaline is highly significant.

However, experiments with Labetalol showed different results. The durg almost blocked, or allowed only a minimal rise of blood pressure with both the doses of Adrenaline (Fig-6).

The mean values with standard error have been presented in Table-01. Alongwith the results obtained from experiments with other Beta Adrenergic Blocking Agents under study.

Statistical significance for the blocking of the rise in mean arterial Blood Pressure by Labetalol has also been calculated by the "t" test of paired variates. The result has been found to be significant statistically.

As regards the depressor activity of adrenergic drugs, Isoprenaline was given in two doses I_1 and I_2 i.e. 1 μg and 2 μg at an interval of 5 minutes. The fall in blood pressure was recorded (Figure-02). When the blood pressure had returned to normal the Beta Adrenergic Blocking Agent under study was given in a dose of 2.5 mg/kg intravenously. The same two doses of Isoprenaline were repeated at the same intervals. This procedure was repeated in six different animals for each Beta Adrenergic Blocking Agents under study.

It was seen that Propranolol blocked the effect of the smaller dose, while the effect of the bigger dose was reduced to about one fourth. (Fig-3).

Timolol reduced the effect of the smaller dose to about one third, while the effect of the bigger dose was reduced to one half only. (Fig-4).

Table-1 Modification of the pressor response of adrenaline by the beta adrenergic blocking agents. Effect of Adrenaline A1 1μg on the mean arterial Blood Pressure

Beta Adrenergic Blocking Agents 2.5 mg/kg	Average change in Blood Pressure in mmHg with Standard error		"t" Value	"P"
	Control Response	Test Response		
Propranolol	+ 16 ± 0.77	+ 39 ± 1.12	16.91	< 0.01
Timolol	+ 15 ± 0.52	+ 36 ± 0.86	21.00	< 0.01
Atenolol	+ 18 ± 0.45	+ 42 ± 1.24	18.18	< 0.01
Labetalol	+ 16 ± 0.86	+ 3 ± 0.52	13.00	< 0.01

Average change in Blood Pressure in mmHg with Standard error

Effect of Adrenaline A2 2μg on the mean arterial Blood Pressure

Beta Adrenergic Blocking Agents 2.5 mg/kg	Average change in Blood Pressure in mmHg with Standard error		"t" Value	"P"
	Control Response	Test Response		
Propranolol	+ 28 ± 0.97	+ 56 ± 1.34	15.76	< 0.01
Timolol	+ 25 ± 1.03	+ 52 ± 1.48	15.00	< 0.01
Atenolol	+ 38 ± 0.68	+ 46 ± 1.36	5.26	< 0.01
Labetalol	+ 26 ± 0.86	+ 8 ± 0.36	19.56	< 0.01

Table2 Modification of the depressor response of isoprenaline by the beta adrenergic blocking agents.

Effect of Isoprenaline II 1μg on the mean arterial Blood Pressure

Beta Adrenergic Blocking Agents 2.5 mg/kg	Average change in Blood Pressure in mmHg with Standard error		"t" Value	"P"
	Control Response	Test Response		
Propranolol	- 14 ± 0.52	- 1 ± 0.16	23.64	< 0.01
Timolol	- 14 ± 0.80	- 5 ± 0.52	9.47	< 0.01
Atenolol	- 25 ± 0.73	- 6 ± 0.52	21.35	< 0.01
Labetalol	- 14 ± 0.45	- 0 ± 0	31.11	< 0.01

Effect of Isoprenaline 12 2μg on the mean arterial Blood Pressure

Beta Adrenergic Blocking Agents 2.5 mg/kg	Average change in Blood Pressure in mmHg with Standard error		"t" Value	"P"
	Control Response	Test Response		
Propranolol	- 41 ± 1.29	- 10 ± 0.58	21.98	< 0.01
Timolol	- 32 ± 0.93	- 17 ± 0.82	12.10	< 0.01
Atenolol	- 48 ± 0.93	- 12 ± 0.58	33.03	< 0.01
Labetalol	- 37 ± 0.77	- 0 ± 0	48.05	< 0.01

Atenolol reduced the effect of both doses of Isoprenaline to about one fourth of its values. (Fig-5).

Labetalol showed a very strong blocking effect to the depressor response of both the dose of Isoprenaline, (Fig-6).

The average derived from results, for all the four Beta Adrenergic Blocking Agents are presented in Table-02, and are shown graphically in Fig-7 and 8.

The value of "t" were calculated by the "t" test for paired vairates, between the values of control and test response in presence of the Beta Adrenergic Bloc king Agents.

Statistical significance of the results obtained for the Beta Adrenergic Blocking Agents under study was calculated. The modifying effect of the Beta Adrenergic Blocking Agents on the depressor activity of Isoprenaline was found to be highly significant

Discussion

We have observed in our experiments that the Beta adrenergic blocking agents modify the pressor and depressor response to adrenaline and Isoprenaline respectively. Two doses of adrenaline 1.25 μg and 2.5 μg were given intravenous to anaesthetised dogs before and after the intraveneous administration of 2.5 mg/kg of the Beta adrenergic blocking agent under study. The rise in blood pressure produced by both the doses was seen to be almost doubled in presence of propranolol, Timolol and Atenolol. This increase in the pressor response to adrenaline has been found to be highly significant ($P < 0.01$) in case of these three Beta adrenergic blocking agents.

As regards the depressor activity of Isoprenaline, the fall in blood pressure produced by 1 μg and 2 μg of Isoprenaline has been found to be completely or partially blocked by the intravenous administration of 2.5 mg/kg of Propranolol, Timolol or Atenolol.

Since Labetalol is known to have alpha blocking activity also, the pressor response to adrenaline was modified in a different manner – the drug almost blocked, or allowed only a minimal rise of blood pressure with both the doses of adrenaline similarly it showed a very strong blocking effect the depressor response of both the doses of Isoprenaline.

Modification of the pressor and depressor responses of adrenaline and Isoprenaline by Beta Blockers have been demonstrated in experimental models, as well as in healthy volunteers and as cardiovascular emergencies The results of our study are in agreement with duties reported on experimental animals[9,1,5]. Modification of canine mean arterial pressure was studied[11]; Propranolol significantly inhibited (50%) of the mean arterial pressure response produced by Isoprenaline infusion which is consistent with our results. Protective effects of Propranolol and Atenolol have been reported in rats treated with cardiotoxic doses of Isoprenaline[6] from cardionecrogenic action of Isoprenaline.

Effects of Propranolol and Atenolol[10], Propranolol and Labetalol[2], during adrenaline infusion in healthy volunteers was studied. Beta-selective Atenolol interfered very little with the haemodynamic response, to adrenaline, whereas a non-selective Beta Blockers changed it to a pure pressor response.

A potentially serious drug interaction between epinephrine and Propranolol has been reported in[3] resulting in profound hypertension and bradycardia.

Similar adverse effects of epirephrine when given to patients taking Propranolol have been reported in [8].Another case has been reported[7] where a hypertensive emergency was induced by excessive ingestion of Pseudoephedrine. This hyperadrenergic state was effectively controlled by Labetalol. Similarly, Labetalol has been suggested for the control of cocaine-induced hypertension[4].In conclusion we can say that the results of our experiments, on the modification of pressor and depressor responses of Adrenaline and Isoprenaline are in agreement with the results of most of the references given above.

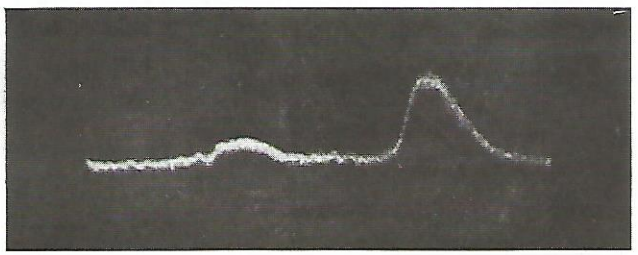

Fig. 1 Effect of adrenaline 1.25μg and 2.5μg/kg i.v. on the blood pressure of anaesthetised dog.

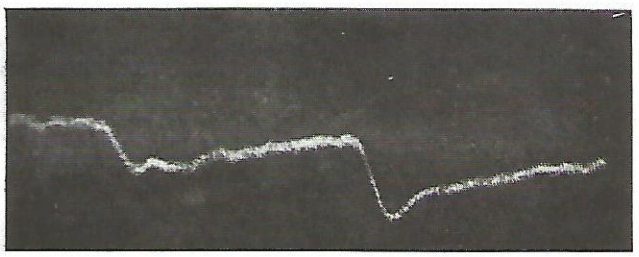

Fig. 2. Effect of adrenaline 1μg and 2μg/kg i.v. on the blood pressure of anaesthetised dog.

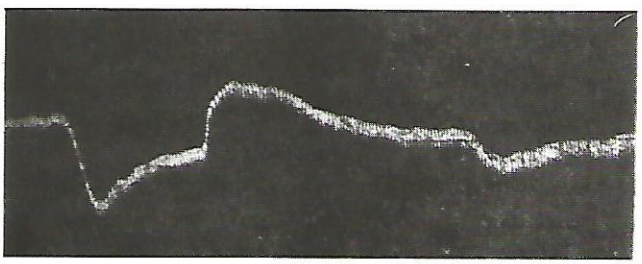

Fig.3. Modification of the pressor response of Adrenaline (1.25μg/kg) and depressor response of Isoprelanline (2μg/kg) by Propranolol2.5mg/kg in anaesthetised dog.

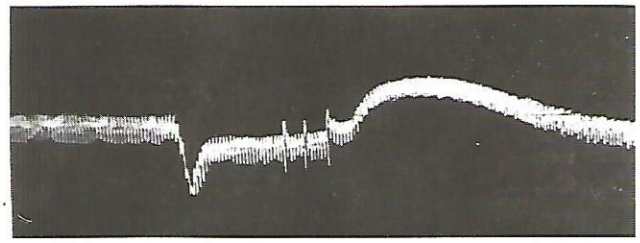

Fig.4. Modification of the pressor response of Adrenaline (1.25µg/kg) and depressor response of Isoprelanline (2µg/kg) by Timolol 2.5mg/kg in anaesthetised dog.

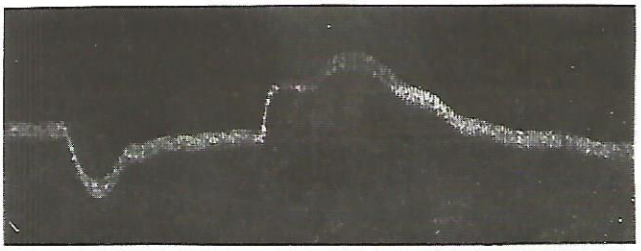

Fig.5. Modification of the pressor response of Adrenaline (1.25µg/kg) and depressor response of Isoprelanline (2µg/kg) by Atenolol 2.5mg/kg in anaesthetised dog.

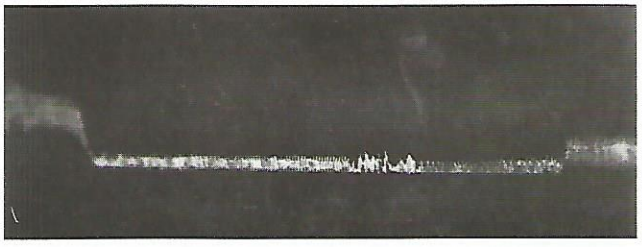

Fig.6. Modification of the pressor response of Adrenaline (1.25µg/kg) and depressor response of Isoprelanline (2µg/kg) by Labetalol 2.5mg/kg in anaesthetised dog.

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