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Lack of inter-action between propranolol and mebanazine

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It has been suggested that treatment with monoamine oxidase inhibitors should be withdrawn 2 weeks before commencing treatment with an adrenergic β-receptor blocking drug e.g. propranolol. Experiments in anaesthetized cats have failed to unmask any undesirable property of propranolol following amine oxidase inhibition. Furthermore, combined treatment with both types of drug reduced the cardiovascular responses to intravenous tyramine and amphetamine. The pressure response to intraduodenal tyramine was no greater in animals treated with both drug types compared with that in cats receiving amine oxidase inhibitor alone, whereas the tachycardia was much reduced.

POTENTIATION of the pressor responses to indirectly acting sympathomimetic amines is a well recognized phenomenon following inhibition of monoamine oxidase. As a consequence of a number of clinical catastrophes, many warnings have been given about the dangers of concomitant administration of other drugs (particularly those affecting the cardiovascular system) and the ingestion of certain foodstuffs. Recently it has been suggested that monoamine oxidase inhibitor therapy should be withdrawn for two weeks before the institution of treatment with propranolol, a specific antagonist of adrenergic β-receptors (Frieden, 1967). The experiments on cats reported here were undertaken to determine whether or not the contra-indication of this particular combination of drugs was truly justified. Mebanazine (α-methylbenzylhydrazine) was chosen as the monoamine oxidase inhibitor because of its potency and lack of sympathomimetic activity (Spinks & Whittle, 1966).

Experimental

METHODS

The experiments were made using cats (1·8–2·8 kg) anaesthetized with chloralose. Blood pressure was recorded from a femoral artery using a pressure transducer and heart rate with a cardiotachometer throughout the experiments. A saphenous vein was cannulated for the intravenous injection or infusion of drugs and in some animals a cannula was also inserted into the duodenum via a midline incision. Five cats were used in each group. Pretreatment with mebanazine at a dose level of 5 mg/kg i.p. was made for 3 days before experiment in those cases where other drugs were given intravenously. For those experiments in which tyramine was given intraduodenally, the cats received 5 mg/kg 18 hr before experiments with an additional 2·5 mg/kg i.d. 2 hr beforehand.

Results

EFFECT OF MEBANAZINE ON RESPONSES TO PROPRANOLOL

The intravenous infusion of propranolol at 5, 10 or 50 μg/kg/min produced a significant bradycardia and a slight reduction in mean blood pressure. The bradycardia, which averaged 21%, was not dose dependent,

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there being no difference between the 5 and 50 μg/kg/min effects. In cats pretreated with mebanazine there was no significant alteration in heart rate or blood pressure as compared to the control cats nor in the responses to propranolol infusion. There was no evidence of any increase in blood pressure following propranolol in any mebanazine treated animal.

EFFECT OF MEBANAZINE AND PROPRANOLOL ON THE RESPONSES TO INTRAVENOUS TYRAMINE AND AMPHETAMINE

Intravenous tyramine over the dosage range of 20–2000 μg/kg produced a dose-dependent series of increments in blood pressure and heart rate (Table 1). In another group of cats which received an intravenous

TABLE 1. CHANGE IN MEAN BLOOD PRESSURE (±S.E. MM HG) AND HEART RATE (±S.E. BTS/MIN) TO ASCENDING DOSES OF TYRAMINE IN UNTREATED CATS AND THOSE RECEIVING EITHER PROPRANOLOL OR MEBANAZINE SEPARATELY OR IN COMBINATION

Dose of tyramine (μg/kg)	Pretreatment							
	None		Propranolol		Mebanazine		Mebanazine and propranolol	
	BP	HR	BP	HR	BP	HR	BP	HR
20	+ 8± 3	− 4± 2	+ 2± 3	− 3± 2	+22±12	0±15	+10±10	+ 1± 2
60	+17± 3	+ 7± 5	+11± 3	− 4± 5	+42±13	+36± 7	+35± 4	+18± 5
200	+32± 5	+10± 9	+28± 6	− 9±10	+78±17	+55±15	+55± 7	+21± 6
600	+79±17	+29±17	+44±11	+ 4±10	+92±15	+65±10	+69± 4	+31± 4
2,000	+107± 8	+66±19	+94±12	+39± 8	+161±12	+100± 9	+78±12	−30±12

infusion of propranolol (5 μg/kg/min) for 30 min before and throughout tyramine dosage there was a smaller increase in blood pressure and heart rate at each dose level. Cats which had been pretreated with mebanazine

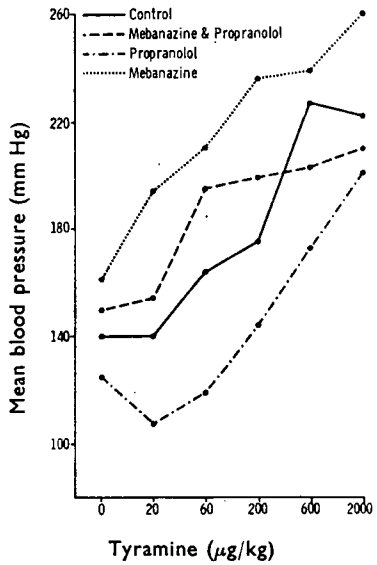

FIG. 1. Final mean blood pressure after intravenous tyramine in cats which had received no medication, propranolol or mebanazine separately or a combination of both drugs.

exhibited potentiated responses throughout the dose range. In those animals receiving a combination of both drugs the responses were larger than those in control cats but lower than in cats pretreated with mebanazine alone. The results have also been presented in a manner comparing the dose of tyramine with the peak blood pressure observed (Fig. 1). It is apparent that the degree of hypertension produced under the influence of both mebanazine and propranolol was at no time greater than that with mebanazine alone.

TABLE 2. CHANGE IN MEAN BLOOD PRESSURE AND HEART RATE AND DURATION OF RESPONSE TO AMPHETAMINE IN UNTREATED CATS AND THOSE RECEIVING EITHER MEBANAZINE ALONE OR BOTH MEBANAZINE AND PROPRANOLOL

		Dose of amphetamine			
		100 μg/kg		200 μg/kg	
	Pretreatment	Change	Duration (min)	Change	Duration (min)
Blood pressure (mm Hg)	None	+39± 8	6±4	+58±10	10± 3
	Mebanazine	+87± 9	15±4	+110±11	17± 2
	Mebanazine and propranolol	+11± 2	8±3	+60± 9	5±3
Heart rate (bts/min)	None	+18±16	8±4	+42± 9	19± 6
	Mebanazine	+47± 9	15±3	+82± 9	30±10
	Mebanazine and propranolol	+ 4± 4	<1	+15± 4	10± 4

The results of similar experiments in which amphetamine was used as the pressor agent are summarized in Table 2. Once again the responses after combined propranolol and mebanazine were appreciably smaller than in cats pretreated with mebanazine alone. It was also apparent that the duration of the responses was reduced to one third that of the mebanazine group in those animals with adrenergic β-blockade.

EFFECT OF MEBANAZINE AND PROPRANOLOL ON THE RESPONSES TO INTRADUODENAL TYRAMINE

Tyramine was administered intraduodenally at a dose of 5 mg/kg, 45 min after beginning an infusion of saline or propranolol (10 μg/kg/min).

TABLE 3. BLOOD PRESSURE AND HEART RATE IN CATS PRETREATED WITH MEBANAZINE BEFORE AND AFTER INTRADUODENAL TYRAMINE FOLLOWING INFUSION OF SALINE OR PROPRANOLOL

		Blood pressure (systolic/diastolic mm Hg)				Heart rate (beats/min)			
Infusion	Cat. No.	Initial	45' after infusion	Peak response to tyr.	Change in systolic	Initial	45' after infusion	Peak response to tyr.	Change
Saline	1	155/125	140/120	250/200	+110	150	162	278	+116
	2	140/95	137/92	235/140	+ 98	225	225	315	+ 90
	3	110/60	92/65	252/166	+160	153	165	294	+129
	4	120/105	120/100	223/200	+103	160	170	280	+110
	5	70/40	60/30	144/124	+ 84	155	150	235	+ 85
	Mean	119/85	110/79	221/166	+111±16	169	174	281	+106±9
Propranolol	1	110/96	93/77	160/143	+ 67	188	123	163	+ 40
	2	105/75	75/45	200/165	+125	135	115	160	+ 45
	3	128/60	122/60	266/195	+144	185	165	210	+ 45
	4	147/105	127/87	220/120	+ 93	202	162	240	+ 78
	5	155/125	160/130	220/190	+ 60	195	148	208	+ 60
	Mean	129/92	115/80	213/163	+98±17	181	143	196	+54±8

The infusion was continued until the end of the experiment. The results are reported in Table 3. Following tyramine there was a steady rise in blood pressure which reached a peak at about 20 min. Heart rate also increased but the peak value was not observed until the peak pressure change was passed. The animals receiving mebanazine alone showed a slightly higher pressor response than those which also received propranolol [systolic values + 111 (84–162) *vs* + 98 (60–144) mm Hg] but the difference was not statistically significant. The changes in heart rate were statistically smaller in the propranolol group ($P < 0.01$). The essential differences in the two groups are illustrated in Fig. 2.

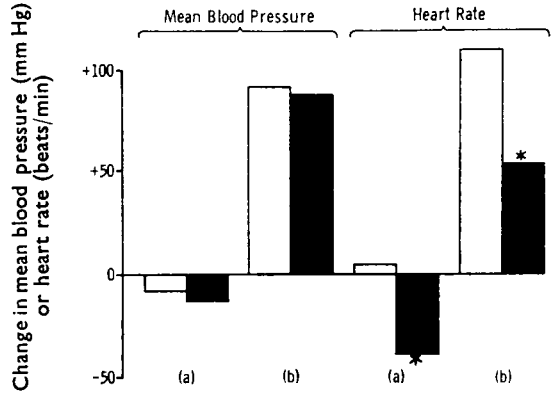

FIG. 2. Average changes in mean blood pressure and heart rate in cats pretreated with mebanazine following the infusion of saline (open columns) or propranolol (solid columns) before (a) and after (b) the intraduodenal administration of tyramine. An asterisk denotes a significant difference between saline and propranolol infused animals ($P < 0.05$).

Discussion

The mechanism by which monoamine oxidase inhibitors potentiate the pressor actions of indirectly acting sympathomimetic amines is now well understood. Substances such as tyramine and amphetamine are good substrates for this particular enzyme which provides the principal means for their metabolism. As a consequence, inhibition of monoamine oxidase leads to both a potentiation and prolongation of their actions. In addition, amine oxidase in the gut wall plays a significant role in the detoxification of such substances following their administration orally as pure drugs or their ingestion as a constituent of certain foodstuffs, notably cheese. Inhibition of amine oxidase leads, therefore, to large amounts of potentially pressor amines passing into the blood stream. In contrast, monoamine oxidase inhibition does not potentiate the hypertensive effects of the natural adrenergic transmitters adrenaline and noradrenaline since these substances are predominantly metabolized by catechol-*O*-methylation.

The present experiments did not provide any evidence that monoamine oxidase inhibition altered the responses to propranolol itself. The only other possibility was that combined administration of both types of

drug would exacerbate the risk of hypertensive crisis, if the contra-indication was truly justified. It is recognized that propranolol will potentiate the pressor responses to adrenaline as a consequence of the blockade of its vasodilator component. Under normal conditions, however, there is no indication that indirectly acting sympathomimetic amines provoke a significant release of adrenaline. The pressor responses to intravenous injection of noradrenaline are reduced by propranolol, due to a reduction in the cardiac component of its action (Shanks, 1966). There is a suggestion that prolonged infusion of noradrenaline may produce a slightly greater pressor response after propranolol (Glover & Hutchison, 1965) but this has not been observed after shorter infusions (Brick, Glover & others, 1966). We have not observed any increase in either the pressor or tachycardia responses when both an amine oxidase inhibitor and propranolol are given together, compared with amine oxidase inhibitor alone, following intravenous injection of tyramine or amphetamine. The reduction in duration of the responses to amphetamine after combined administration of both types of drug may well indicate that its hypertensive action has a major cardiac component following amine oxidase inhibition. Similarly, the pressor responses to intraduodenal tyramine, in a dose equivalent to approximately $\frac{3}{4}$ lb (350 g) of Canadian Cheddar cheese (Blackwell & Marley, 1966) for a 70 kg man, were not potentiated by combined administration of mebanazine and propranolol.

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