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ANTAGONISM BETWEEN CHLORPROMAZINE AND NORADRENALINE IN BLOOD VESSELS OF THE HANDS

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Chlorpromazine (dimethylaminopropyl-*N*-chlorphenothiazine HCl) has a pronounced effect on the circulation in man (Foster, O'Mullane, Gaskell, and Churchill-Davidson, 1954; Duff, McIntyre, and Butler, 1956), causing peripheral vasodilatation as a result of both a central effect and a direct action on the blood vessels (Ginsburg and Duff, 1956). The constrictor response to adrenaline is modified by both intra-arterial and intravenous chlorpromazine (Ginsburg and Duff, 1956); the pressor response to noradrenaline is reduced by intravenous chlorpromazine (Foster *et al.*, 1954). The present investigation is a quantitative study of the effect of intra-arterial chlorpromazine on noradrenaline vasoconstriction in the hands of healthy adults.

METHODS

Twenty-four tests were carried out on ten healthy subjects (nine men and one woman) aged between twenty and thirty-five years. Blood flow in both hands was measured throughout each test by venous occlusion plethysmographs under standard laboratory conditions (Barcroft and Swan, 1953). The flows were calculated and expressed as ml./100 ml. hand volume/min. The general procedure was similar to that previously employed in an analogous study of the action of chlorpromazine and adrenaline (Ginsburg and Duff, 1956). Constrictor responses in the hand to 4-min. infusions of intra-arterial and intravenous noradrenaline were measured first. Noradrenaline was given intra-arterially in doses of 0.125 μg./min. and 0.5 μg./min., and intravenously in a concentration of 10 μg./min. Chlorpromazine was then infused into the brachial artery in a total amount of 1.2 mg., after which the infusions of noradrenaline were replicated in identical order. The course of a typical experiment, as depicted in Fig. 1, consisted first in giving three infusions of noradrenaline, two of which were intra-arterial, the third intravenous; chlorpromazine was then infused intra-arterially, after which the three noradrenaline infusions were repeated. In every test the mean changes in hand blood flow with each infusion were calculated, and analysed by the method described in the previous study of chlorpromazine (Ginsburg and Duff, 1956).

RESULTS

Response to Intra-arterial Noradrenaline Before and After Chlorpromazine

Noradrenaline, 0.125 μg./min.—The effect of chlorpromazine on the constrictor response to noradrenaline was tested in six subjects. A typical experiment is illustrated in Fig. 1. The first infusion of noradrenaline caused a significant reduction (53%) in the mean flow in the test hand. After chlorpromazine (1.2 mg.) had been infused into the brachial artery, the blood flow in the test hand rose considerably; when the infusion of noradrenaline was then repeated, there was only a slight reduction (16%) in flow in the test hand. The results of seven individual tests in which noradrenaline was given intra-arterially before and after the infusion of chlorpromazine are given in Table I. The mean constrictor response to the first infusion of noradrenaline averaged 44% in the seven tests; after the infusion of chlorpromazine the mean response was only 10% (columns [B–E/E]%, Table I). These figures are a measure of the mean decrease in flow in the test hand, expressed as a percentage of the control level of flow in that hand. The percentage constrictor response to noradrenaline was therefore markedly reduced by the infusion of chlorpromazine. A measure of the actual volumetric reduction in flow caused by noradrenaline is obtained from the value of B–E; this may be termed the net constriction. In the seven tests with 0.125 μg./min. noradrenaline the net constriction averaged 3.9 ml. before and 0.7 ml. after chlorpromazine. Thus chlorpromazine reduced the constrictor response to noradrenaline (0.125 μg./min.) both relatively and absolutely.

Noradrenaline, 0.5 μg./min.—The action of chlorpromazine on the constrictor effects of a higher

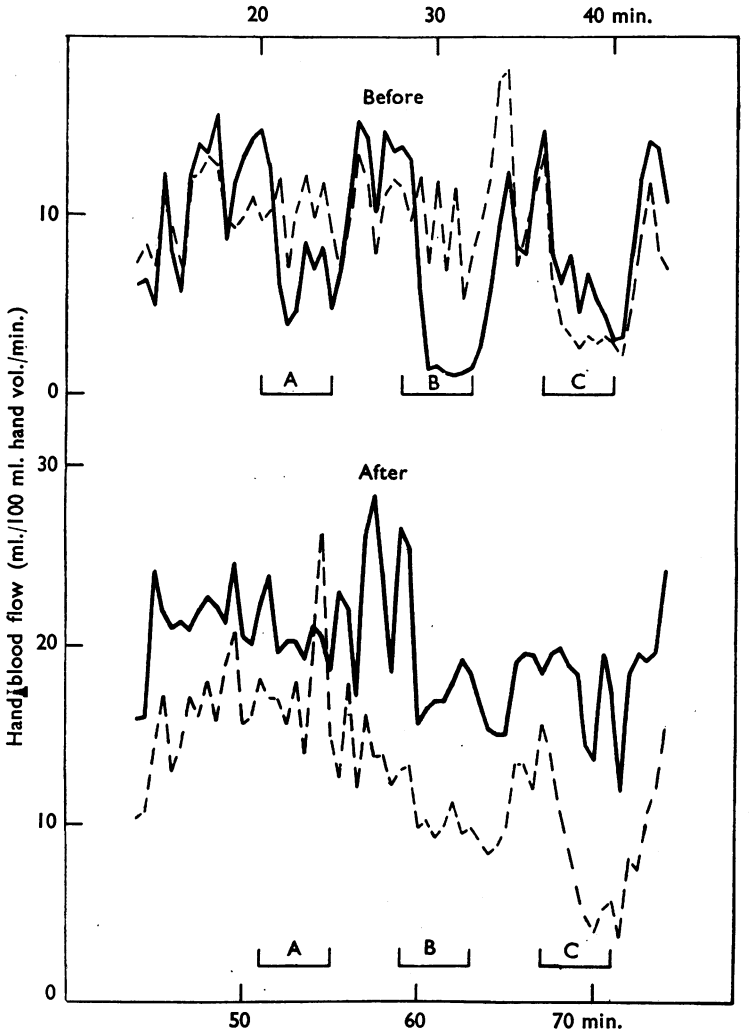

FIG. 1.—Response of hand blood flow in one subject (J. E. ♂) to noradrenaline intra-arterially (A, 0.125 μg./min. for 4 min. and B, 0.5 μg./min. for 4 min.) and intravenously (C, 10 μg./min. for 4 min.) before (upper records) and after (lower records) chlorpromazine (1.2 mg. in 6 min., starting at 44 min. on the record) infused into right brachial artery. Solid lines, right hand; broken lines, left hand.

concentration of noradrenaline (0.5 μg./min.) was examined in ten subjects. The initial constriction was greater with this dose of noradrenaline than with 0.125 μg./min. Thus, in the experiment of Fig. 1, the first infusion of 0.5 μg./min. noradrenaline caused a marked decrease (82%) in flow in the test hand. After the infusion of chlorpromazine, the same dose of noradrenaline caused only a slight decrease (2%) in flow. The detailed results of tests in ten subjects are assembled in Table II. Before chlorpromazine, the percentage reduction in hand blood flow with 0.5 μg./min. noradrenaline averaged 82% in eleven tests; after chlorpromazine, the mean reduction in flow was only 27% (columns [B–E/E]%, Table II). Chlorpromazine clearly caused a marked reduction in noradrenaline vasoconstriction.

The net decrease in flow (B–E) with the initial infusions of 0.5 μg./min. noradrenaline averaged 5.7 ml. whereas after chlorpromazine the net constriction was 3.9 ml. The difference between these means is not significant ($\bar{x}=1.8$, S.E.$=1.4$). The net reduction in flow with 0.5 μg./min. noradrenaline was almost as great after the infusion of chlorpromazine as before it. The percentage constriction was, however, considerably reduced by the chlorpromazine, an effect attributable to the vasodilatation produced by this drug itself. The mean changes in flow are shown diagrammatically in Fig. 2.

Response to Intravenous Noradrenaline Before and After Intra-arterial Chlorpromazine

Noradrenaline was given intravenously in a dose of 10 μg./min. before and after the intra-arterial infusion of chlorpromazine. The first infusion of intravenous noradrenaline reduced the flow in both hands by about the same amount (Fig. 1). After chlorpromazine had been infused into the right brachial artery and the mean flow in that hand had risen, intravenous noradrenaline caused only a slight reduction in flow in the right hand. The second intravenous infusion of noradrenaline caused a marked reduction in flow in the left hand which had not been infused with chlorpromazine. The mean results in six tests with intravenous noradrenaline are summarized in Table III. The mean constrictor response to noradrenaline (10 μg./min.) averaged initially 55% for the right hands and 65% for the left hands (columns [B–A/A]% and [b–a/a]%, Table III). After chlorpromazine had been infused into the right brachial artery, the mean constriction on that side was only 23%; constriction in the left hands, which had not

TABLE I

RESPONSE TO INTRA-ARTERIAL NORADRENALINE (0.125 μG./MIN.) BEFORE AND AFTER INFUSING CHLORPROMAZINE (1.2 MG.) INTO THE BRACHIAL ARTERY

No.	Subject	Before Chlorpromazine					After Chlorpromazine				
		Mean Blood Flow ml./100 ml. Tissue/min.					Mean Blood Flow ml./100 ml. Tissue min.				
		Test Hand		Control Hand		B–E/E%	Test Hand		Control Hand		B–E E%
		A	B	a	b		A	B	a	b	
1	J.E.	12·8	6·4	9·8	10·4	−53	22·2	20·2	17·8	19·3	−16
2	P.J.	6·9	8·5	8·0	12·3	−20	12·7	12·8	16·6	14·9	+12
3	R.D.	7·5	3·6	6·8	6·9	−52	23·9	16·9	16·3	10·2	+13
4	I.D.	8·2	3·8	6·2	6·5	−55	11·7	11·2	12·0	11·6	−01
5	P.J.	13·1	9·9	15·2	13·9	−18	12·7	12·8	16·6	14·9	+12
6	B.B.	3·8	1·2	3·6	2·4	−67	9·4	2·4	4·2	2·9	−63
7	O.R.	7·5	6·1	7·2	10·3	−43	7·8	3·7	6·1	3·9	−26
	Mean	8·2				−44	14·3				−10

A, a, means of six measurements of hand blood flow during 3 min. before noradrenaline in test and control hands respectively; B, b, corresponding means during first 3 min. of noradrenaline period. E=Ab/a.

received chlorpromazine, remained about the same and averaged 55%. The net constriction (B–A) in the test hands with intravenous noradrenaline was 3.9 ml. before, and 4.1 ml. after, chlorpromazine: the difference between those means is not significant ($\bar{x}$=0.2, S.E.=1.4). The infusion of chlorpromazine into the brachial artery thus caused vasodilatation in the corresponding hand and a reduction in the percentage response in that hand to intravenous noradrenaline; chlorpromazine had no appreciable effect on the circulation in the opposite hand.

DISCUSSION

The present study confirms that chlorpromazine causes vasodilatation in the hand, when infused into the brachial artery (Ginsburg and Duff, 1956). This dilator action must therefore be taken into consideration in evaluating other effects of the drug. The results of the experiments designed to assess antagonism to noradrenaline have been analysed to distinguish these actions.

When the results of all the intra-arterial infusions of noradrenaline were assembled, it was found that the initial infusions had reduced the hand blood flow from a mean of 8.0 ml. to 2.9 ml., indicating a net reduction of 5.1 ml. (Fig. 3). After giving chlorpromazine, the blood flow in the infused hands increased to a mean level of 13.5 ml., a rise of almost 70%. The subsequent infusion of noradrenaline caused a reduction in mean flow from the now increased resting level of 13.5 ml. to 10.9 ml., a net decrease of only 2.6 ml. The difference between the mean values for the net vasoconstriction (5.1 ml. before chlorpromazine and 2.6 ml. after) is clearly due to chlorpromazine

TABLE II

RESPONSE TO INTRA-ARTERIAL NORADRENALINE (0.5 μG./MIN.) BEFORE AND AFTER INFUSING CHLORPROMAZINE (1.2 MG.) INTO THE BRACHIAL ARTERY

No.	Subject	Before Chlorpromazine					After Chlorpromazine				
		Mean Blood Flow ml./100 ml. Tissue/min.					Mean Blood Flow ml./100 ml. Tissue min.				
		Test Hand		Control Hand		B–E/E%	Test Hand		Control Hand		B–E E%
		A	B	a	b		A	B	a	b	
1	O.R.	7·3	0·4	6·1	6·4	−95	9·3	8·7	7·1	8·8	−22
2	B.B.	3·2	0·4	3·0	2·8	−87	9·7	2·3	2·4	2·5	−77
3	J.E.	13·3	2·1	10·7	9·2	−82	23·2	17·0	13·7	10·3	−02
4	R.D.	6·8	0·7	6·4	5·1	−87	27·8	20·2	22·6	16·7	−01
5	I.D.	7·5	2·4	4·8	5·5	−72	10·9	9·7	14·9	9·9	+33
6	P.J.	11·9	1·3	16·9	5·5	−67	17·2	12·4	11·4	8·8	−05
7	D.A.	9·8	2·5	14·4	12·9	−72	12·3	6·6	14·9	16·0	−50
8	C.W.	7·5	0·9	7·8	7·2	−87	14·5	5·8	7·2	6·2	−53
9	R.C.	3·9	0·9	9·9	10·6	−79	19·9	14·2	16·6	16·4	−28
10	N.M.	7·5	1·2	6·3	6·7	−82	16·2	11·8	8·6	10·7	−42
11	D.A.	12·9	0·3	15·7	11·7	−97	12·3	6·6	14·9	16·0	−50
	Mean	8·3		9·3	7·6	−82	15·7		12·2	11·1	−27

A, a, means of six measurements of hand blood flow during 3 min. before noradrenaline in test and control hands respectively; B, b, corresponding means during first 3 min. of noradrenaline period. E=Ab/a.

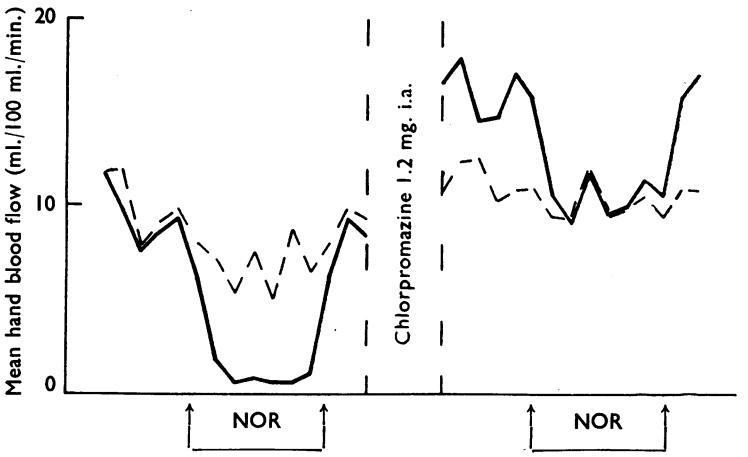

FIG. 2.—Mean blood flow in test hands (solid lines) and control hands (broken lines) during intra-arterial infusions (NOR) of noradrenaline (0.5 μg./min. for 4 min.) before and after intra-arterial chlorpromazine (1.2 mg. in 6 min.).

and presumably reflects a real antagonism to the infused noradrenaline.

When the response to noradrenaline is expressed as the percentage reduction in hand blood flow following its administration, the inhibitory effect of chlorpromazine on noradrenaline vasoconstriction is even greater. Thus the mean percentage vasoconstriction caused by noradrenaline was 82% initially and only 27% after chlorpromazine. The resting level of flow was, of course, higher after the infusion of chlorpromazine (Table II and Fig. 2). The reduction of noradrenaline vasoconstriction by chlorpromazine must therefore be partly attributed to the direct dilator action of chlorpromazine on the blood vessels.

There are several possible explanations for this direct dilator action. It might be due to a blocking of sympathetic constrictor impulses at nerve endings, or to an action on circulating constrictor substances; alternatively the drug might act directly on arteriolar muscle. The extent to which the dilator effect of chlorpromazine depends upon its antagonism to noradrenaline cannot be determined until all the factors responsible for normal vascular tone have been evaluated. The evidence that noradrenaline is intimately concerned in sympathetic transmission favours the possibility that the vasodilatation from chlorpromazine involves an action on sympathetic nerve endings in the vessel walls.

The pressor effect of noradrenaline is reduced by systemic chlorpromazine in animals (Courvoisier, Fournel, Ducrot, Kolsky, and Koetschet, 1953; Kopera and Armitage, 1954) and man (Foster *et al.*, 1954). But this action is comparatively slight, and noradrenaline is clinically effective in the treatment of prolonged hypotension after systemic chlorpromazine (Preston and Wishart, 1954). It is therefore reasonable to infer that the inhibitory effect of chlorpromazine on noradrenaline vasoconstriction is less marked in vascular beds other than those of the hands.

Chlorpromazine has little or no specific action in man against injected adrenaline (Ginsburg and Duff, 1956); the reduction in the constrictor response to adrenaline could be wholly accounted for by the vasodilatation produced by the chlorpromazine. It would therefore appear that in the vessels of the hand chlorpromazine is more effective against noradrenaline than against adrenaline. In laboratory animals, however, chlorpromazine reduces the pressor action of adrenaline to a much

TABLE III

RESPONSE TO INTRAVENOUS NORADRENALINE (10 μG./MIN.) BEFORE AND AFTER INFUSING CHLORPROMAZINE (1.2 MG.) INTO THE BRACHIAL ARTERY

No.	Subject	Before Chlorpromazine Mean Blood Flow ml./100 ml. Tissue/min.						After Chlorpromazine Mean Blood Flow ml./100 ml. Tissue/min.					
		Test Hand		Control Hand		B–A/A%	b–a/a%	Test Hand		Control Hand		B–A/A%	b–a/a%
		A	B	a	b			A	B	a	b		
1	J.E.	10·6	5·9	10·9	3·2	−44	−71	18·5	17·7	12·9	6·7	−04	−48
2	R.D.	8·4	4·1	9·2	3·2	−51	−65	20·2	16·3	11·2	6·8	−19	−39
3	R.C.	4·4	1·9	12·3	4·9	−57	−60	18·5	14·4	19·5	6·9	−22	−65
4	R.C.	3·8	1·8	9·9	4·3	−53	−57	24·6	18·3	21·4	9·0	−26	−58
5	N.M.	8·2	3·5	8·7	3·0	−57	−66	12·8	9·3	5·2	2·2	−27	−58
6	N.M.	7·5	2·5	6·8	2·0	−67	−71	15·2	9·1	9·6	2·8	−46	−60
	Mean					−55	−65					−23	−55

A, a, means of six measurements of hand blood flow during 3 min. before noradrenaline in test and control hands respectively; B, b, corresponding means during first 3 min. of noradrenaline period.

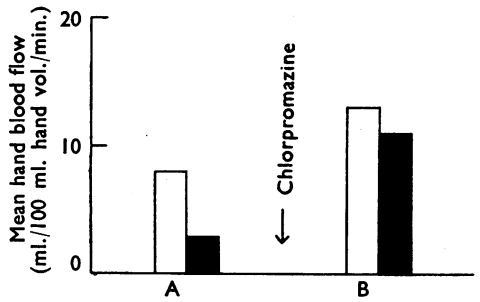

FIG. 3.—Mean blood flow in test hands before (open rectangles) and during (solid rectangles) intra-arterial infusions of noradrenaline (0.125 μg./min. and 0.5 μg./min. for 4 min.) before (A) and after (B) intra-arterial chlorpromazine (1.2 mg. in 6 min.).

greater extent than that of noradrenaline (Courvoisier *et al.*, 1953; Kopera and Armitage, 1954). These differences are less likely to be due to a variation in species than to a different action of the drug on various parts of the vascular tree. Of even greater interest, perhaps, is the curious difference in the effect of chlorpromazine on the differential response of the same vascular bed to adrenaline and noradrenaline.

SUMMARY

1. The effects of intra-arterial chlorpromazine on noradrenaline vasoconstriction in the hands of healthy adults have been assessed by venous occlusion plethysmography.

2. The infusion of chlorpromazine into the brachial artery caused a marked reduction in the constrictor response in the hand to noradrenaline. This effect has been shown to be largely attributable to the direct vasodilator action of chlorpromazine, but partly also to a specific antagonism to infused noradrenaline.

3. Some implications of these findings are briefly discussed.

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