Inhibition of Levarterenol by Intra-Arterial Phenoxybenzamine in Man

By JEAN GINSBURG, M.A., B.M., B.CH. (Oxon.), and ROBERT S. DUFF, M.D., M.RCP.

The infusion of 1.2 mg. phenoxybenzamine into the brachial artery of healthy adults was followed by a marked reduction in constrictor responses in the corresponding hands to infused levarterenol and to sympathetic stimuli.

The vasodilator effect of phenoxybenzamine (Dibenylline; Dibenzyline; N-N-dibenzylichloroethylamine hydrochloride) recently has been shown to depend considerably on purely peripheral actions of the drug in man.1,2 In addition it was found that the intra-arterial administration of phenoxybenzamine reduced or abolished constrictor responses to epinephrine in the hand.2 The present investigation is a similar study of the effect of phenoxybenzamine on peripheral constrictor responses to levarterenol (noradrenalin, norepinephrine) in healthy adults.

METHODS

Peripheral circulatory effects of levarterenol and of phenoxybenzamine were studied in 11 healthy adults between the ages of 10 and 30 years. Changes in blood flow were measured in both hands by venous occlusion plethysmography under standard laboratory conditions.3

In each experiment, constrictor responses to intra-arterial and to intravenous levarterenol were determined before and after infusing 1.2 mg. phenoxybenzamine into the brachial artery, according to the procedure detailed in the earlier study.2 The mean vascular change produced by each infusion of the drug was calculated by a method4,5,6 that made possible an assessment of both the relative and the net effects of the levarterenol and of the influence of phenoxybenzamine on these responses.

RESULTS

Effect of Intra-Arterial Phenoxybenzamine on the Constrictor Response in the Hand to Intra-Arterial Levarterenol

Intra-Arterial Levarterenol, 0.125 μg./min.

The first such infusion into the right brachial artery was associated with a decrease in blood flow in the test right hand but with no change in mean flow in the control left hand. When, later, phenoxybenzamine was given into the same artery the blood flow in the right hand almost doubled, without any appreciable change in the level of flow in the left hand.

On repeating this concentration of levarterenol, the right hand exhibited little or no reduction in flow.

In 7 tests with this dose of levarterenol the mean relative or percentage change of flow in the test hands was initially a decrease of 55 per cent. After the phenoxybenzamine injection, the mean change in flow with this same dose of levarterenol was only 4 per cent. The net vasoconstriction during these infusions of levarterenol, as measured by the volumetric reduction of flow, averaged initially 4.1 ml./100 ml. hand volume/min. and only 0.4 ml. after phenoxybenzamine. Thus the constrictor response in the hand to intra-arterial injection of levarterenol (0.125 μg./min.) was virtually abolished after 1.2 mg. phenoxybenzamine had been infused into the corresponding brachial artery.

Intra-Arterial Levarterenol (0.5 μg./min.).

The first intra-arterial infusion of the larger dose of levarterenol profoundly reduced the circulation through the test hand in every subject, the average fall being from 9.0 to 2.3 ml./100 ml. hand volume/min. (table 1, columns A and B). After the administration of phenoxybenzamine, the blood flow in the test hands rose to more than twice the original level, and when the second infusion of levarterenol was given, only a slight reduction in flow occurred (from 19.5 to 16.7 ml./100 ml./min., table 1). Account being taken of incidental fluctuations in the noninfused
control hands, the net reduction in flow (B-E, table 1) in the test hands averaged 7.2 ml./100 ml./min. with the first levarterenol infusion, and only 3.9 ml. with the second, after the phenoxybenzamine infusion. Initially the mean percentage reduction in flow due to the levarterenol was 80 per cent, while that produced by the second dose of levarterenol (0.5 μg./min.) was only 17 per cent (table 1, columns (B-E)/E per cent). Thus, after infusing phenoxybenzamine intra-arterially, the constrictor response to this concentration (0.5 μg./min.) of levarterenol were greatly weakened but not abolished (fig. 1).

Effect of Intra-Arterial Phenoxybenzamine on the Constrictor Response in the Hand to Intravenous Levarterenol

In general, the first intravenous infusion of levarterenol (10 μg./min.) lowered the blood flow in both hands by about the same amount. After phenoxybenzamine had been given into the right brachial artery, a second intravenous infusion of levarterenol had little or no effect on the blood flow in the right hand but reduced the flow in the left hand by about the same amount as before. The mean level of flow in the right hand had of course risen with the infusion of the blocking drug.

In 6 tests, the preliminary infusions of intravenous levarterenol reduced the mean flow in the test hands by 46 per cent and in the control hands by 55 per cent. After 1.2 mg. phenoxybenzamine had been infused into the right brachial artery the mean change in flow in the test hands during the second intravenous infusion of the sympathomimetic drug was only 4 per cent, whereas in the control hands the reduction in flow was much the same as before (58 per cent).

Thus the constrictor response to intravenous levarterenol was practically abolished in hands that had received phenoxybenzamine, but not in the control hands.

DISCUSSION

These experiments have demonstrated the effectiveness of intra-arterial injection of phenoxybenzamine in antagonizing constrictor effects of levarterenol in man. Inhibition of the latter in the hand was not, however, complete, for with the larger dose injected intra-arterially, the constrictor response, though greatly lessened, was not entirely abolished. Since the constrictor effect of the same concentration of epinephrine was completely abolished by intra-arterial phenoxybenzamine,2 it might be concluded that this blocking agent is more effective against epineph-

**Table 1.** Effect on Hand Blood Flow of Intra-arterial Levarterenol (0.5 μg./min.) before and after Infusing Phenoxybenzamine (1.2 mg.) into the Brachial Artery

<table>
<thead>
<tr>
<th>No</th>
<th>Subject</th>
<th>Test hand (ml./100 ml hand vol./min.)</th>
<th>Control hand (ml./100 ml hand vol./min.)</th>
<th>Mean (B-E)/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D.B.</td>
<td>7.8 1.2 14.3 13.1</td>
<td>8.2 1.4 22.9 22.2</td>
<td>-83</td>
</tr>
<tr>
<td>2</td>
<td>J.E.</td>
<td>18.4 6.3 24.9 22.2</td>
<td>5.3 1.3 10.5 14.0</td>
<td>-89</td>
</tr>
<tr>
<td>3</td>
<td>E.M.</td>
<td>14.5 3.9 10.5 14.0</td>
<td>12.4 2.4 18.9 20.8</td>
<td>-93</td>
</tr>
<tr>
<td>4</td>
<td>J.O.</td>
<td>7.8 1.2 9.6 7.5</td>
<td>2.5 0.6 10.4 11.1</td>
<td>-89</td>
</tr>
<tr>
<td>5</td>
<td>L.M.</td>
<td>4.1 0.6 4.0 6.8</td>
<td>14.2 10.9 8.5 7.2</td>
<td>-89</td>
</tr>
<tr>
<td>6</td>
<td>J.R.</td>
<td>4.1 0.5 3.4 2.6</td>
<td>7.3 0.4 14.2 10.9</td>
<td>-85</td>
</tr>
<tr>
<td>7</td>
<td>J.B.</td>
<td>6.0 0.6 3.0 4.4</td>
<td>10.2 8.0 3.2 4.4</td>
<td>-85</td>
</tr>
</tbody>
</table>

Columns A, a, Means of 6 measurements of hand blood flow during 3 min. immediately before infusing levarterenol in test and control hands respectively.

Columns B, b, corresponding means during first 3 min. of levarterenol period.

Columns C, Ab/a.
PHENOXYBENZAMINE AND LEVARTERENOL

Fig. 1. Mean change in hand blood flow of 7 subjects during intra-arterial infusion of levarterenol (0.5 μg/min for 4 min.) before (open rectangles) and after (solid rectangles) intra-arterial infusion of phenoxybenzamine Dibenzyline (1.2 mg in 6 min.).

Fig. 2. Mean blood flow in test hands before (open rectangles) and during (solid rectangles) intra-arterial infusion of levarterenol (0.5 μg/min for 4 min.) during initial period (on left) and after intra-arterial infusion of 1.2 mg. phenoxybenzamine (on right).

rime than it is against levarterenol. Normally, however, the latter amine causes a greater reduction in mean vascular caliber in the hand than does the former. One may therefore conclude that the blocking drug is at least as much an inhibitor of levarterenol as it is of epinephrine. And indeed, in the cat, Nickerson, Henry and Nomaguchi found that phenoxybenzamine lessened the response of the nictitating membrane to levarterenol much more than it lessened the response to epinephrine, while the pressor response to levarterenol was blocked at least as effectively as the pressor response to epinephrine.

Figure 2 shows that the resting-hand blood flow initially averaged 9.5 ml. and fell to 2.3 ml. during the infusion of levarterenol, which indicates a net volumetric reduction in flow of 7.2 ml. After injection of phenoxybenzamine, when the resting level of flow had increased by about 11 ml. to a mean of 20.6 ml., levarterenol caused a reduction in flow of only 3.1 ml. Thus phenoxybenzamine influenced the net volumetric response to levarterenol as well as the relative or percentage vasoconstriction. The results of individual tests showed further that there was no close relationship between the increase in hand flow caused by phenoxybenzamine and the subsequent weakening of the constrictor response to levarterenol. The inhibitory effect of phenoxybenzamine on vasoconstrictor response was therefore not directly determined by the increase in vascular caliber caused by this blocking agent.

In view of the importance of levarterenol in sympathetic transmission, the influence of phenoxybenzamine on sympathetic activity was also investigated. A study was made of the effects of stimuli that normally cause marked reflex vasoconstriction in the hands, such as unexpected noise or the application of ice to the forehead. After phenoxybenzamine injection these stimuli still evoked vasoconstrictor responses in both hands, but these were much less marked on the side previously infused with the blocking agent. In 5 tests, unexpected sensory stimuli caused an immediate and marked fall in flow in the control hands (from 14.1 ml. to only 5.2 ml./100 ml./min.), while at the same time the blood flow in hands previously infused with phenoxybenzamine was only slightly reduced (from 23 ml. to 19.7 ml./100 ml./min.). If levarterenol is the effector substance released by the activity of sympathetic constrictor nerves, it may be inferred from the results of these experiments that the effective amount released in response to the auditory and tactile stimuli was such as to produce a local concentration in the vascular bed of the hand that was equivalent to that obtained by introducing it into the brachial artery at a rate between 0.125 and 0.5 μg./min.

Downloaded from http://circres.ahajournals.org/ by guest on July 8, 2017
No doubt the dilator action of phenoxybenzamine depends to an important extent on an inhibitory effect on the sympathetic nervous system. But this is not the sole factor, for vasodilation may be produced by intra-arterial phenoxybenzamine in extremities surgically deprived of their sympathetic nerves. In these conditions vasodilation may be due to the inhibition of circulating epinephrine and levarterenol, or to some direct action of the drug on arteriolar muscle.

**Summary**

In healthy adults the effects of phenoxybenzamine on peripheral vasoconstriction produced by infused levarterenol and by sympathetic nervous activity have been assessed by a plethysmographic method. After the infusion of 1.2 mg of phenoxybenzamine into the brachial artery the constrictor responses in the corresponding hand to intra-arterial and intravenous levarterenol and to sympathetic stimuli were all considerably reduced. The physiologic and pharmacologic implications of these findings are discussed.

**Acknowledgment**

The authors have pleasure in expressing their gratitude to Professor Henry Barcroft for his encouragement and valuable criticism, to colleagues and medical students who acted as subjects and to Mr. G. T. Hales and Miss R. Palmer for their efficient technical assistance.

Certain expenses were defrayed by a grant from the Endowment Fund of St. Thomas Hospital. Levarterenol ('Levophed') was supplied by Bayer Products, Ltd. Phenoxybenzamine (Dibenzyline) was supplied by Smith, Kline and French International Company.

**Summario in Interlingua**

Le effectos de phenoxybenzamina super le vasoconstriction peripheric resultante del infusion de levarterenol e del activitate sympathico-nervose esseva evatutate in adultos normal per medio de un metodo plethysmographic. Post le infusion de 1,2 mg de phenoxybenzamina in le arteria brachial, le responsas constrictori al administration intra-arterial e intra-venose, in le mano al latere correspondente, de levarterenol et etiam a stimuli sympathetic esseva considerabilemente reduce. Le signification physiologic e pharmacologic de iste constatationes es discutite.

**References**

Inhibition of Levarterenol by Intra-Arterial Phenoxybenzamine in Man
JEAN GINSBURG and ROBERT S. DUFF

Circ Res. 1958;6:751-754
doi: 10.1161/01.RES.6.6.751

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1958 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/6/6/751