The Direct Renal Vascular Effects of Epinephrine and Norepinephrine before and after Adrenergic Blockade

By MERRILL P. SPENCER, M.D., ADAM B. DENISON, JR., M.D., AND HAROLD D. GREEN, M.D.

By use of a noncannulating electromagnetic flowmeter the direct vasoconstrictor response of the dog renal vasculature to intra-arterial epinephrine was found to be but slightly greater, weight for weight, than that of norepinephrine. No dilation phase to their reactions was found before or after Ilidar, and this adrenergic blocking drug failed to dilate the renal vasculature in four out of five dogs in the anesthetized and operated state.

By direct intra-arterial injections, the response of the muscle vascular bed to L-epinephrine in dogs has been found to be a double one, that is, an initial vasoconstriction followed by vasodilation, while L-norepinephrine and sympathetic nerve stimulation give essentially a vasoconstrictor response. These investigators found that the cutaneous vascular bed responds both to drugs and to sympathetic nerve stimulation by pure vasoconstriction without reversal by the adrenergic blocking drugs. They report that all responses in both these vascular beds are blocked by the adrenergic blocking agents, Ilidar, Dibenzyline, Regitine and Priscoline. So-called reversal of the epinephrine response in the muscle vasculature arises because the constrictor response is blocked at a lower dose than the dilator response.

This study was carried out, first, to determine the direct effects of L-epinephrine and L-norepinephrine on renal vasomotor tone. Second, we wished to study the blocking action of Ilidar on these responses in regard to efficacy of blockade and possible reversal effects. Third, we were interested in any direct dilator effect of adrenergic blockade which might indicate a tonic sympathetic vasoconstriction in the kidneys of anesthetized dogs. Ilidar, the newest member of the adrenergic blocking agents, was the drug of choice because in humans it has the fewest side effects of the four blocking drugs listed, yet in dogs it is capable of blocking completely the constrictor responses of epinephrine, norepinephrine and sympathetic nerve stimulation in skin and muscle and has a wide dose range between epinephrine reversal and norepinephrine blockade in muscle vascular beds.

METHODS

Left or right renal blood flow and femoral arterial pressure were measured directly and continuously in 10 pentobarbitalized dogs (12 to 15 Kg.) during the intra-arterial injection of 1, 3 and 10 μg. doses of L-epinephrine (hydrochloride) and L-norepinephrine (base). In five dogs these doses were repeated after progressively increased intra-arterial doses of Ilidar.

For the measurement of blood flow a new development of the electromagnetic flowmeter was used. The following drugs were kindly supplied to us by the companies indicated: Adrenaline hydrochloride by Parke-Davis Co., Detroit, Mich.: Levophed bitartrate by Winthrop-Stearns, Inc., New York, N. Y.: Ilidar (formerly Ro2-3248) by Hoffmann-LaRoche, Inc., Nutley, N. J.

* Ilidar (azapetine phosphate) (6-allyl-6,7-dihydro-5H-dibenzo[e, c] azepine-H3PO4); Dibenzyline (phenoxybenzamine-HCl) (N-phenoxy-isopropyl-N-benzyl-p-chlorethylamine-HCl); Regitine (phentolamine-HCl) (2-[[N-(m-hydroxyphenyl)-p-toluidino]methyl]-2-imidazoline-HCl); Priscoline (Tolazoline-HCl) (2-benzyl-4,5-imidazoline-HCl).
TABLE 1.—Comparison of Renal Vasoconstrictor Actions of Intra-arterial l-Epinephrine and l-Norepinephrine

<table>
<thead>
<tr>
<th>I.A. Dose</th>
<th>No. Paired Observations</th>
<th>Avg. ml Blood Shunted By</th>
<th>Mean Diff. (l-epi. - l-nor.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9</td>
<td>58.5 33.8 24.5 21.2</td>
<td>0.30</td>
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<tr>
<td>3</td>
<td>9</td>
<td>69.8 58.4 11.3 10.6</td>
<td>0.36</td>
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<tr>
<td>10</td>
<td>10</td>
<td>217.0 148.7 68.3 18.4</td>
<td>0.005</td>
</tr>
</tbody>
</table>

These observations were made in nine experiments, four of which were adrenergic blockade experiments reported here. Each norepinephrine injection was immediately prior to, or immediately following, the paired epinephrine injection of the same animal.

RESULTS

Direct Effects of l-Epinephrine and l-Norepinephrine on the Renal Vasomotor Tone.†

†Mepesulfate (Treburon) is a heparin-like anticoagulant obtained from Hoffmann-LaRoche, Inc., Nutley, N. J.
TABLE 2.—Adrenergic Blocking Doses of Ilidar in the Kidney

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Ilidarnone</td>
<td>l-epinephrine 1 µg.</td>
<td>l-norepinephrine 1 µg.</td>
<td>Ilidarnone</td>
<td>l-epinephrine 3 µg.</td>
<td>l-norepinephrine 3 µg.</td>
</tr>
<tr>
<td>C.J. 6</td>
<td>0.1</td>
<td>1</td>
<td>1</td>
<td>0.1</td>
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<td>3</td>
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<tr>
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<td>0.3</td>
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<td>8</td>
<td>1</td>
<td>10</td>
<td>7</td>
<td>30</td>
<td>5</td>
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<td>0.3</td>
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<td>3</td>
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<td>50</td>
<td>10</td>
<td>30</td>
<td>55</td>
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<tr>
<td>C.J. 6</td>
<td>26</td>
<td>26</td>
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Non-blocking = largest dose of Ilidar tried which failed to block completely. Blocking = smallest dose which completely blocked responses. Estimated = logarithmic average of doses which completely blocked response.

Both sympathetic amines gave pure vasoconstrictor responses so far as the net vasomotor tone was concerned, with no dilator phase being seen at any dose. Table 1 shows the degree of constriction brought about by paired 1, 3 and 10 µg. doses of l-epinephrine and l-norepinephrine previous to use of Ilidar. Since mean arterial pressure was unaffected by these doses, the effect on vasomotor tone was analyzed by integrating the change in the volume flow and response time into a single factor expressing the volume of blood shunted away from the kidney by each drug action. On the average, l-epinephrine had a slightly greater vasoconstrictor effect than l-norepinephrine, but calculations of the probabilities that the observed differences were not due to chance established statistical significance only to the 10 µg. doses.

The Blocking Action of Ilidar on the Renal Vasoconstrictor Effects of l-Epinephrine and l-Norepinephrine. From the original records from one experiment (fig. 1) it is apparent that stepwise increases in the dose of Ilidar progressively blocked the vasoconstrictor actions of both adrenergic drugs. As expected, progressively larger doses were required to block the larger doses of the sympathetic amines. Table 2 shows the doses necessary to effect complete blockade. In no experiment did Ilidar unmask any vasodilator effect of either l-epinephrine or l-norepinephrine.

Direct Effect of Ilidar on the Renal Vasomotor Tone. The results in five anesthetized dogs showed that up to 3 mg. of Ilidar injected directly into the renal artery usually had no effect on the renal vasomotor tone, while doses higher than 3 mg. had a constrictor action. With the exception of one experiment, terminated early on account of profuse uncontrolled bleeding, Ilidar failed to elicit a dilation response when given in doses capable of blocking amounts of epinephrine and norepinephrine which constricted the renal vessels to the point of zero flow.

DISCUSSION

Our method of studying rapid responses of renal blood flow to the intra-arterial injection of drugs eliminates reflex neurogenic and hormonal effects which obscure the direct action of pressor and depressor drugs injected intravenously. In addition, renal autonomous vasomotor mechanisms resulting from changes in the systemic arterial pressure are eliminated.

Our finding that epinephrine has but little more direct renal vasoconstrictor effect than norepinephrine is apparently in disagreement with Ahlquist's finding6 that "it required five to ten times more levartenol than epinephrine to produce an equivalent degree of renal vasoconstriction by intra-arterial injection." Two factors help to resolve this and other discrepancies reported by various investigators who compared these two drugs. First, we compared norepinephrine base with equal weights of epinephrine hydrochloride while Ahlquist made his injections on an equimolar basis. This factor could, however, reduce the apparent strength of epinephrine, compared with
that of norepinephrine, by only 23 per cent. The second and more important explanation of the discrepancy comes from an analysis of the dosage response curves of the two sympathetic amines. When the molar doses are plotted against the average volume of blood shunted away from the kidney, the epinephrine response is consistently greater, but it is also apparent that, when stating the magnitude of the difference, it matters greatly whether one compares doses necessary to give the same response, as Ahlquist did, or whether one compares the responses obtained at the same dose, as our experiments do. This factor is most apparent at the lower dose ranges used. Thus with 0.045 micromols of epinephrine base (1 µg. epinephrine hydrochloride or 0.846 µg. epinephrine base) it requires 300 per cent more norepinephrine to give the same response, but 0.045 micromols of norepinephrine base (0.70 µg.) will give 60 per cent of the response given by 0.045 micromols of epinephrine. Because of the variability of individual responses, the difference between the drugs measured by the latter method does not appear statistically significant. At the 10 µg. dose level, the difference between the two drugs by the latter method becomes greater and that of the former becomes smaller.

Since intra-arterial Ilidar, in doses capable of blocking strong adrenergic constriction of epinephrine and l-norepinephrine, caused no vasodilation following its injection into four out of five dogs, these results fail to demonstrate consistent tonic sympathetic effect on the renal vasculature during the anesthetized and operated state. There is no reason to suspect that the renal nerves were not functional in each experiment, since the application of the flowmeter was far from a denervation procedure.

SUMMARY AND CONCLUSIONS

The actions of Ilidar on the innervated renal vasculature and on the direct renal responses to intra-arterial injections of l-epinephrine and l-norepinephrine were studied in five pentobarbitalized dogs. Renal blood flow was measured with a noncannulating development of the electromagnetic flowmeter, the magnet-electrode assembly of which was applied directly to the surgically exposed artery. Doses of 1, 3 and 10 µg. of the two catechol amines were administered intra-arterially before and after progressively increasing doses of the adrenergic blocking agent. The following conclusions are reached:

When injected directly into the arteries of innervated kidneys, l-epinephrine has a greater vasoconstrictor action than that of l-norepinephrine. This difference is more apparent at 10 µg. than at 1 and 3 µg. doses.

The adrenergic blocking drug, Ilidar blocks but does not reverse the constrictor reactions of epinephrine and norepinephrine.

Neither sympathomimetic amine has a renal vasodilator effect either manifest or latent. It is therefore concluded that the renal vasculature is incapable of responding directly to the vasodilator potentiality of epinephrine.

Intra-arterial injections of Ilidar cause no vasodilation in the renal vascular circuit of anesthetized and operated dogs when blood loss has not been large.

REFERENCES
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