Effect of Chlorothiazide on Response of Renal Vascular Bed to Vasoactive Substances

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It seems fairly well established that chlorothiazide reduces the rise in arterial pressure produced by intravenously injected norepinephrine and levarterenol in the normotensive animal\(^1\) and in the normotensive\(^2\) and hypertensive human.\(^3-7\) Chlorothiazide has also been shown to increase the effectiveness of a variety of antihypertensive agents and the reduction of arterial blood pressure in the sympathectomized hypertensive patient. However, there is no information which indicates whether the attenuation of the catecholamine response is mediated through an effect upon cardiac output or through an effect upon blood vessels. For this reason, the acute effect of chlorothiazide upon the response of the renal vascular bed to locally injected, naturally occurring vasoactive agents was studied in a preparation which eliminated the factor of change in blood flow. In addition, the study permitted an examination of the effect of chlorothiazide per se upon renal vascular resistance.

**Methods**

The effect of increasing the renal arterial blood concentration of chlorothiazide upon renal vascular resistance and responsiveness was studied in the anesthetized dog. This was accomplished by holding constant the blood flow to the left kidney and by observing the effect of intraarterial infusion of an isosmotic solution of chlorothiazide on perfusion pressure and on the response of perfusion pressure to norepinephrine, levarterenol, Val-5-angiotensin II, acetylcholine, CaCl\(_2\), KCl, and MgCl\(_2\).

Twenty-one dogs, weighing 10 to 15 Kg., were anesthetized with intravenously administered sodium pentobarbital (33 mg./Kg.). Heparin sodium (5 mg./Kg.) was administered intravenously. Taking care not to disturb the left kidney, the abdominal aorta was occluded with a Potts clamp placed between the left and right renal arteries, and the lumbar vessels were tied. This diverted the entire output from the pump through the left kidney. Blood flow was adjusted to an average value of 74 ml/min. (range 46 to 123 ml/min.) which produced a mean perfusion pressure of approximately 80 mm. Hg. This provided an average blood flow of 0.53 ml/min./gm. of kidney tissue. Pressure was measured just proximal to the glass cannula with a pressure transducer connected to a direct-writing oscillograph recorder. The preparation has been described in detail in an earlier communication.\(^8\)

In 11 dogs, an isosmotic solution of NaCl was infused into the perfusion system at rates of 0.12, 0.25, 0.49, 1.23, 2.47, and 4.94 ml/min., in that order. Each rate was maintained for 30 seconds and perfusion pressure continuously recorded. The sequence was repeated except that an isosmotic solution of chlorothiazide in saline (1.5 mg./ml.) was substituted for the NaCl. This provided an average chlorothiazide concentration of 0.02 mg/ml. (range 0.01 to 0.03 mg/ml.) in the perfusion system. After completion of the above, the NaCl solution was again infused at 2.47 ml/min., and the pressure changes to 1-ml. single bolus intraarterial injections of isosmotic solutions of norepinephrine (1 \(\mu\)g. base/ml.), levarterenol (1 \(\mu\)g. base/ml.), Val-5-angiotensin II (0.1 \(\mu\)g./ml.), acetylcholine (1 \(\mu\)g. base/ml.), KCl (298 mOsm./Kg.), MgCl\(_2\) (302 mOsm./Kg.), and CaCl\(_2\) (305 mOsm./Kg.) were recorded. This sequence was repeated while infusing the isosmotic chlorothiazide solution at the same rate.

To determine whether time per se influenced the responses, the single bolus injection experiment was repeated in six additional animals, except that the second infusion was also NaCl. Four additional animals were studied to determine duration of effect of chlorothiazide upon the responses.

\(^*\)Determined by the Fiske osmometer.
The area under the renal arterial pressure tracings was measured with a planimeter and expressed as mm.2. This took into account both the intensity and duration of the response to the vasoactive substances.

Results

Figure 1 presents the average change in renal perfusion pressure as a function of the infusion rate of chlorothiazide and NaCl in 11 dogs. Perfusion pressure was not affected by either infusion. In the same 11 animals, perfusion pressure increased following injection of L-epinephrine, levarterenol, Val-5-angiotensin II, and CaCl2, decreased following injection of acetylcholine and MgCl2, and was affected irregularly by KCl. Urine flow was approximately 0.2 ml./min. during NaCl infusion, and during chlorothiazide infusion there was a two- to threefold increase.

Figures 2 and 3 show that the responses to L-epinephrine, levarterenol, and Val-5-angiotensin II during infusion of NaCl were significantly greater than the responses during infusion of chlorothiazide. On the other hand, the response to MgCl2 during infusion of NaCl was significantly less than during infusion of chlorothiazide.

In the second series of experiments designed to determine whether time per se influences the responses to the vasoactive agents, in this preparation, it was found that the responses to L-epinephrine, levarterenol, and Val-5-angiotensin II were equally great during both the first and second infusions of isosmotic NaCl (fig. 4).

In a third series of four animals, L-epinephrine, levarterenol, and Val-5-angiotensin II were injected during infusions of isosmotic NaCl, isosmotic chlorothiazide, and isosmotic NaCl in that sequence. The period of time between infusion of chlorothiazide and the final NaCl solution was 10 minutes. The responses were greatly attenuated during infusion of chlorothiazide, but returned almost to the control values in the time which elapsed between discontinuance of the chlorothiazide and start of the final NaCl infusion.

Discussion

These studies show that infusion of chlorothiazide into the renal artery does not acutely affect resistance to blood flow through the renal vascular bed. It does, however, immediately attenuate the constriction produced by local injection of L-epinephrine, levarterenol, and Val-5-angiotensin II and potentiates the dilation produced by local injection of MgCl2. Further, these altered responses seem to disappear within a few minutes of stopping the chlorothiazide infusion. These findings suggest that chlorothiazide attenuates the pressor response to intravenously injected catecholamines, at least in part, through an effect upon blood vessels.

The altered responses of various pressor and depressor substances by chlorothiazide is a familiar and much discussed phenomenon. The factors of diminished plasma volume and decreased total exchangeable sodium do not seem to have any significant role in the acutely altered responses observed with chlorothiazide in this investigation.

It is difficult to explain the observations that chlorothiazide per se has no effect upon renal vascular resistance, whereas it attenuates the activity of naturally occurring constrictors and potentiates the activity of naturally occurring dilators. The absence of an effect of chlorothiazide on renal resistance cannot be explained by assuming that the renal bed was maximally dilated because the bed did respond with dilation to MgCl2 and...
The effects of intra-arterial injections of 1 µg of l-epinephrine, levarterenol, and Val-t-angiotensin II on renal perfusion pressure during infusion of saline and chlorothiazide solutions at 2.47 ml/min. in the same animal. Average renal blood flow was constant at 74 ml/min. The time interval between administration of pressor agents during NaCl and chlorothiazide infusion was 10 minutes. Arrows indicate time of injection of the pressor agents.

The average effect of injections of various vasoactive agents upon area under renal perfusion pressure tracing during saline and chlorothiazide infusions at 2.47 ml/min. One ml of injectate was delivered in each instance, and renal blood flow was constant. The two infusions were separated by a period of 10 minutes. Bars represent ± one standard error of the mean.

Effect of time per se on the responsiveness of the renal vascular bed to l-epinephrine, levarterenol, and angiotensin. The two saline infusions were separated by a period of 10 minutes. Bars represent ± one standard error of mean.

Moreover, observations in a higher resistance bed, the dog foreleg, utilizing the same technique, show that resistance...
is unaffected by chlorothiazide except at infusion rates in excess of 150 mg./min.\textsuperscript{9}

It is possible that the explanation may be related to the plasma concentration of the injected vasoconstrictors and vasodilators. The administration of these agents by single bolus intra-arterial injection, even in the small amounts used in this study, undoubtedly more than double their local plasma concentrations. It may well be that the effect of chlorothiazide on the activities of these agents is manifest only at levels well in excess of those which occur normally.

Summary

In the anesthetized dog, administration of an isosmotic solution of chlorothiazide into the renal artery failed to affect renal vascular resistance but did acutely attenuate the constriction produced by intra-arterial injection of l-epinephrine, levarteralenol, and Val-5-angiotensin II and potentiated the dilation produced by intra-arterial injection of MgCl\textsubscript{2}.

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Circ Res. 1962;11:283-286
doi: 10.1161/01.RES.11.2.283

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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