The Lack of Effect of Oral Doses of Cinchona Alkaloids on the Circulation of Dogs with Renal Hypertension

A Contrast to Their Action in Neurogenic Hypertension

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The effect of repeated oral doses of quinine and quinidine on the circulation of dogs with renal hypertension was studied with measurements of arterial blood pressure and renal hemodynamics. Alkaloid concentrations up to the toxic range had little effect on the blood pressure or renal blood flow. It is pointed out that this lack of effect is in contrast to the vasodilator action of these agents in normal and neurogenic hypertensive dogs. These experiments are interpreted as constituting support for the thesis that the cinchona alkaloids have their vasodepressor effect by virtue of a blockade of sympathetic neuromuscular vasomotor junctions.

It has been shown in this laboratory that orally administered cinchona alkaloids cause renal vasodilatation in normal dogs without much change in arterial blood pressure. In dogs with experimental neurogenic hypertension these alkaloids cause a fall in the blood pressure as well as renal vasodilation when administered in repeated oral doses. For a long time it has been known that when these drugs are given intravenously there is a sharp fall in blood pressure. Nelson, in a series of papers published in 1927, investigated this phenomenon and concluded that the depressor effect of intravenous quinine and quinidine was due to peripheral vasodilatation brought about partly by blockage of the vasomotor nerve endings and partly by a direct action on the arteriolar smooth muscle. He demonstrated that these drugs would antagonize the circulatory effects of epinephrine or splanchnic nerve stimulation. We have recently confirmed these observations, with measurements of the effective plasma concentrations of alkaloid.

It occurred to us that it might be possible, in dogs with renal hypertension, to assay the importance of the depressor action of these drugs directly on the smooth muscle of the arterioles or on the myocardium as separate from their sympatholytic effects. In such animals the hypertension is regarded as due to a humoral agent acting directly on the smooth muscle of arterioles with some stimulating action on the myocardium but with little contribution from sympathetic vasoconstrictor nerves. The experiments reported here show the lack of effect of repeated oral doses of quinine and quinidine in dogs with renal hypertension in contrast to the decrease in blood pressure seen with the same regimen in dogs with experimental neurogenic hypertension.

Procedure

The experimental animals used in this work were female dogs, of the mongrel type, ranging in weight from 9 to 13.6 Kg. After control observations on blood pressure, the dogs were made hypertensive according to the method of Goldblatt. Briefly this method consists of constricting the main renal artery on each side by applying to it a metal clamp. The operation was done in two stages allowing time after the first clamp was applied for the animal to recover before clamping the artery on the other side.

After the final operation, if the dog showed a sustained rise in mean blood pressure, it was considered to be a renal hypertensive animal. The 5 dogs used showed increases of 18, 33, 36, 43, and 69 per cent and had mean blood pressures ranging from 150 to 220 mm. Hg. All experiments, with the exception

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of those on one dog, were done within one to three months after the animals became hypertensive. The one exception had repeated surgery over the course of a year in a vain attempt to increase its hypertension.

Direct measurement of the arterial blood pressure was carried out in the following manner. The unanesthetized dog was strapped loosely on its back to a dog board. Using 1 per cent procaine as a local anesthetic, the femoral artery was punctured with a 19 gage hypodermic needle which was connected to a tube filled with 5 per cent sodium citrate solution leading to a mercury manometer. After observing the mean pressure as registered by the mercury manometer, the needle was connected to a Hamilton membrane manometer and the blood pressure recorded photographically.

In preparation for doing renal clearances, 10 ml. of a mixture of 5 per cent creatinine and 2 per cent pamaonhippururate were given intravenously as a "priming" dose. Twenty ml. of the same solution were given subcutaneously into the loose skin on the flanks of the dog. Creatinine clearances were used as a measure of the glomerular filtration rate and para-

mighthippururate (PAH) clearances were taken as a measure of the effective renal plasma flow. The dog was catheterized, and 30 minutes after the priming dose, the bladder was washed out with water, the urine discarded, and urine collection begun. Four urine samples were collected at 10 minute periods. No attempt was made to induce water diuresis in the dogs, but the bladder was washed out with water at the end of each collection period. Blood samples were taken at intervals for analyses of the concentrations of PAH, creatinine, and cinchona alkaloids.

After the control clearances, doses of one of the cinchona alkaloids were started. The usual procedure was to give four capsules of 15 mg. per Kg. on the first day and four or five capsules at approximately four hour intervals for the next two days, except that a lapse of about 10 to 12 hours occurred at night. This dosage schedule assured a level as high as or higher than that maintained in similar experiments on neurogenic hypertensive dogs.

During the period of drug administration, the dog's blood pressure was checked once or twice daily, and renal clearance measurements were made on different occasions while the dog was under the influence of the drug. When the drug was discontinued, at least a two day interval was allowed for complete disappearance of alkaloid from the plasma and blood pressure and clearances were again measured. The time usually required for an experiment was six days.

The analyses of plasma and urine concentrations of PAH were done according to the methods described by Smith and collaborators, and creatinine concentrations were determined by the alkaline piperate method of Folin and Wu. Quinine and quinidine concentrations in the plasma were analyzed according to the method of Brodie and Udenfriend.

Results

The results of our experiments on all 5 dogs were essentially the same and are indicated in the accompanying graphic summaries of typical experiments.

In figure 1 it can be seen that a plasma concentration as high as 8 to 10 mg. per liter was achieved by repeated oral doses of quinidine sulfate as shown in the lower portion of the graph. In spite of the high concentration of alkaloid the blood pressure of this hypertensive dog showed little change as indicated by the height of the bars in the central part of the graph. In the upper section of the graph we have plotted the clearances of PAH, represented by the entire bar, and the clearances of creatinine as indicated by the black portion of each bar. Each bar represents an average of four clearance periods. The effective renal plasma flow (PAH clearance) and the filtration rate (creatinine clearance) increased in this experiment during the interval of the experimental period but without relation to the plasma alkaloid concentration.

In figure 2 a very similar experiment is shown except that quinine sulfate was administered. In this experiment the plasma alkaloid concentration was not so high as that shown in figure 1 but still in the range which caused a marked fall in the blood pressure of dogs with neurogenic hypertension. In this experiment there was an apparent renal hyperemia during the administration of the drug, like that in normal dogs, but this was not typical.

In figure 3 the contrast is shown between the effect of the cinchona alkaloids on dogs having renal hypertension and the effect on those with neurogenic hypertension. Blood pressures as percentages of the control pressure are plotted against plasma alkaloid concentrations. The control pressure in each case was taken as the average of the pressure just before the drug was started and that following withdrawal of the drug and its elimination from the plasma. The data from the dogs with renal hypertension (the solid symbols) indicate very little effect of the cinchona alkaloids on the blood pressure even at levels as high as 10 mg. per liter. There seems to be a slight hypertensive effect at low
Fig. 1. The effect of repeated oral doses of quinidine sulfate on the blood pressure and renal clearances of a dog with renal hypertension. In the upper section of the graph, creatinine clearances are represented by the darkened part of the bars and PAH clearances by the entire bars.

Fig. 2. The effect of repeated oral doses of quinine sulfate on the blood pressure and renal clearances of a dog with renal hypertension.

Concentrations of quinine and a slight hypotensive effect at all concentrations of quinidine. In contrast, the data on the neurogenic hypertensive dogs, taken from the work of Hiatt.
and shown as open symbols, show a marked downward trend of the blood pressure with increasing plasma concentrations of both alkaloids, apparent in spite of the wide scatter which is characteristic of blood pressure measurements in this type of preparation. It is obvious that the depressor effect of quinidine is greater than that of quinine.

In the beginning it was our intention to measure renal blood flow and glomerular filtration rate on all dogs before and after applying clamps to the renal arteries. But when it became apparent that in our hands the percentage of successful preparations was not high, we abandoned the control observations. However, we have compared the PAH and creatinine clearances of our hypertensive postoperative dogs with Houck's statistical analyses of these measurements in normal dogs. Our mean values for both of the clearances, on the basis of body weight, were approximately 63 percent of his mean values. In both the normal and hypertensive series, there was a very large scatter. The dogs used in our experiments showed no consistent change in renal hemodynamics with administration of cinchona alkaloids (another contrast with the neurogenic hypertensive dogs), but there was a general tendency for both effective renal plasma flow and glomerular filtration rate to increase with time after clamping the arteries.

The pulse rate, as in normal and neurogenic hypertensive animals, increased slightly or re-

![PLASMA ALKALOID CONCENTRATION IN MG./LITER](image)

**Fig. 3.** The effect of oral quinine and quinidine on the blood pressure of renal hypertensive dogs in contrast with their effect on the blood pressure of dogs with neurogenic hypertension. One hundred percent represents the average of two control blood pressure measurements, one preceding drug administration and the other, after the drug had been eliminated.

**DISCUSSION**

In considering how oral cinchona alkaloids cause a lowering of the blood pressure in dogs with neurogenic hypertension, one thinks of three possibilities: a sympatholytic action decreasing vasomotor tone, a relaxing action directly on arteriolar smooth muscle, or a depressor action on the heart. Of course there might be any combination of these three mechanisms. The first of these possible mechanisms
has been demonstrated by the antagonism of quinine and quinidine to the circulatory effects of epinephrine and splanchnic nerve stimulation. The other two mechanisms apparently are not important as indicated by the above described lack of effect of the alkaloids (even at toxic plasma concentrations) on the blood pressure of dogs with renal hypertension. This view assumes that the maintenance of an arterial hypertension is evidence against an important depression of either arteriolar smooth muscle or myocardium.

Ferrer and her collaborators reported that a single oral dose of quinidine sulfate (0.8 Gm.) in human subjects with and without cardiovascular diseases caused, in most instances, a fall in arterial pressure, but cardiac output, as determined by right heart catheterization, did not show any measurable change in those patients in whom there was a normal control output. Those patients with low cardiac outputs and elevated right ventricular systolic pressures responded with a shift toward normal values. The authors suggest that the fall in arterial blood pressure following quinidine is due largely to peripheral vasodilatation, but they also present electrocardiographic evidence for an effect on the myocardium.

It seems pertinent to mention that the plasma concentrations of cinchona alkaloids obtained in our experiments are not out of the range encountered in clinical use of these drugs. Sokolow and Edgar have reported that 75 per cent of a series of 30 patients with auricular fibrillation converted to normal rhythm at plasma concentrations between 4 and 9 mg. per liter. In a similar study Kalmansohn and Sampson found somewhat higher levels at the time of conversion. The minimum plasma quinine concentration in man necessary to suppress a malaria infection has been observed to be from 5 to 10 mg. per liter, according to the species and strain of the parasite, while quinidine is effective at somewhat lower plasma concentrations.

SUMMARY

Female dogs were made hypertensive according to the renal ischemia method of Goldblatt. Repeated oral doses of quinine and quinidine sulfate were administered and the effect on blood pressure and renal clearances noted. A comparison was made between the effect of the drugs on renal and neurogenic hypertensive dogs.

1. The blood pressure of renal hypertensive dogs was not significantly lowered at plasma alkaloid concentrations as high or higher than those which caused a sustained depressor effect on the blood pressure of neurogenic hypertensive dogs.

2. Mean renal clearances (creatinine and PAH) of the renal hypertensive dogs were reduced to 63 per cent of normal values. No consistent change due to the alkaloids was observed though the clearances tended to increase with time after the renal arteries were clamped.

3. The maintenance of blood pressure at plasma alkaloid concentrations as high as 10 mg. per liter indicated that neither arteriolar smooth muscle nor myocardium was markedly depressed and strengthens our impression that the depressor action of these drugs in normal animals is primarily at sympathetic neuromuscular vasomotor junctions.

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