EFFECTS OF REPEATED ORAL DOSES OF QUININE AND QUINIDINE ON THE BLOOD PRESSURE AND RENAL CIRCULATION OF DOGS WITH EXPERIMENTAL NEUROGENIC HYPERTENSION

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It has been shown in this laboratory that single oral doses of the cinchona alkaloids will cause an increase in renal blood flow and glomerular filtration rate in normal dogs (7). This effect lasts for several hours and occurs without significant change in arterial blood pressure. In the investigations reported in this paper we have studied the effect of repeated oral doses of quinine and quinidine given over a period of several days on the circulation of normal dogs and of dogs with experimental neurogenic hypertension.

METHODS

A sustained hypertension was obtained in 4 dogs by excision of both carotid sinuses and division of the cervical vago-depressor-sympathetic nerve trunk on one side and the depressor nerve of the opposite side, according to the technic of Bouckaert as described by Grimson (6). These dogs, together with several normal dogs, were observed before, during and after a period of several days in which they received two to four daily doses of 10 to 15 mg/kg of quinine or quinidine sulfate. The experiments were carried out at different intervals varying from one to 16 months after the surgical operation.

Mean arterial blood pressure was measured by puncture of the femoral artery with a 20-gauge hypodermic needle connected through a tube filled with 5 per cent sodium citrate solution to a mercury manometer. One per cent procaine without epinephrine was injected into the tissues around the artery before the puncture was made. Readings of pressure were taken a minute or two after the needle was introduced, when the pressure seemed to be fairly steady.

The renal clearance of sodium p-aminohippurate (PAH) was determined as a measure of the effective renal plasma flow. The creatinine clearance was determined as a measure of the glomerular filtration rate. PAH concentrations in plasma and urine were determined by the method of Smith et al. (9) while creatinine concentrations were analysed by the alkaline picrate method of Folin and Wu (5). These agents were administered subcutaneously to obtain satisfactory plasma concentrations.

Quinine and quinidine concentrations in the plasma were determined by the method of Brodie and Udenfriend (3).

It was our usual practice to give four doses the first day and three doses on subsequent days with a 10-hour interval between the last dose of one day and the first dose of the next day. After the control observations, most of the measurements were made before the first dose of the day, at the time when plasma concentrations were at the daily minimum, but occasional measurements were made at shorter intervals after a dose of alkaloid. The observations were continued for at least two days after the drugs had been discontinued.

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RESULTS

The results of our experiments on all 4 dogs were essentially the same and are indicated in the accompanying graphical summaries of typical experiments (fig. 1).

a. Plasma Alkaloid Concentrations. Most of these fell within the range of 1 to 4 mg/l. These levels were effective in causing the changes described below but were not toxic as indicated by the normal behavior and appetite of the dogs. After a few doses the plasma concentration was well maintained between doses, even during the 10-hour overnight period. Two doses a day did not maintain plasma concentrations in the effective range, but three doses a day seemed to be adequate.

b. Blood Pressure. In the normal dogs there was little change in the mean arterial pressure. In the dogs with neurogenic hypertension there was a marked fall in blood pressure, in most cases closely approaching their normal preoperative pressures. After the second day of administration of the alkaloids the depressor effect was well maintained between doses. When the drugs were discontinued the blood pressure gradually returned to the original hypertensive levels as the plasma concentrations decreased. This recovery was usually complete in about 36 hours. Quinidine had a more marked effect on the blood pressure than quinine.

c. Renal Circulation. In most of the normal dogs receiving repeated doses of cinchona alkaloids, as in the experiments with single doses reported previously...
(7), the renal plasma flow and the glomerular filtration rate increased, the former more than the latter. In most instances the effect lasted during the period of administration of the drug. Unlike the single dose experiments (7), the present data, with repeated doses, shows that quinine causes a greater renal hyperemia than quinidine.

Essentially the same effects on renal circulation were observed in hypertensive dogs. In spite of a considerable fall in arterial blood pressure there was no decrease in renal plasma flow and in most instances there was a definite increase, especially with quinine.

d. Heart Rate. In most of the normal dogs an increase in heart rate occurred after administration of the alkaloids. The hypertensive dogs which maintain a rapid heart rate (10) showed either a further acceleration of the rate or no change under the influence of the drugs.

DISCUSSION

In considering the mechanism by which the cinchona alkaloids reduce the blood pressure of our dogs with neurogenic hypertension there is not much help to be found in the literature. Most of the reported experiments have dealt with the depressor effect of the alkaloids injected intravenously (which is much more drastic than when the same amount of alkaloid is administered orally) and the plasma concentration of the drugs was not measured. There was, and still is, a controversy over whether or not most of the depressor effect is due to cardiac depression or to peripheral vasodilatation. Nelson (8) who reviewed the old literature felt that the action of these alkaloids is due to peripheral vasodilatation. He thought this action to be due in part to depression of the vasomotor endings and in part to an action directly on the smooth muscle of the blood vessels.

Nelson also demonstrated the antagonism of quinine and quinidine for the circulatory effects of epinephrine. We have succeeded in verifying this in experiments which will be reported later. Dreisbach and Hanzlik (4) have studied the converse relationship, i.e., the antagonism by epinephrine of the depressor effects of intravenous quinine.

Bing, Thomas and Waples studying the circulation of dogs with experimental neurogenic hypertension found evidences of increased sympathetic tone as indicated by increased cardiac output, increased renal vascular resistance and increased blood flow through the forelimb (2). These investigators also studied the effects of the adrenolytic dioxane derivatives 883 and 933 F on dogs with neurogenic hypertension and found a delayed fall in blood pressure due largely to a diminished cardiac output with a decrease in heart rate (1).

All we can say definitely at this time is that these cinchona alkaloids cause a sustained decrease in blood pressure in dogs with neurogenic hypertension. At least part of their effect is due to vasodilatation as indicated by the renal hyperemia and the well-known cutaneous flushing (8) which follows the administration of these drugs. Independent investigation of possible effects of these drugs on cardiac output are currently being undertaken.
SUMMARY

Oral doses of quinine or quinidine of the order of 10 to 15 mg/kg administered to dogs three times a day for several days had the following effects: a) in normal dogs a sustained renal hyperemia (as measured by clearance methods) without much change in blood pressure; b) in dogs with neurogenic hypertension, a sustained fall in the blood pressure without any decrease in renal circulation. With quinine there is actually an increase in renal blood flow. Quinidine had a greater depressor effect on the blood pressure than quinine. These effects were achieved with plasma concentration of cinchona alkaloid in the range of 1 to 4 mg/l.

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REFERENCES