ACUTE TOXICITY OF PARENTERAL CHLOROQUINE

By

N.K. BHIDE[1], M. ASHWINI KUMAR[2], AND U. K. SHETH

From the Pharmacological Research Unit of the C. S. I. R. Department of Pharmacology, Seth G. S. Medical College, Bombay

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Chloroquine is an important synthetic antimalarial agent of established value; it is also used for the treatment of amoebic hepatitis, other parasitic infestations and certain connective tissue diseases. Although oral administration is preferred, it may occasionally have to be given parenterally, e. g. in an acute emergency or if the patient is vomiting.

While studying the effect of chloroquine on urine output of anaesthetized dogs, one of us (N. K. B.) noticed profound and fatal hypotension after intravenous injection of quantities comparable to the human therapeutic dose. Serious reactions after chloroquine have also been reported in the clinical literature (Harris, 1955, 1957; Kjaer, 1955; Sanghavi, 1956). The present work was designed to determine the mechanism by which chloroquine produces its acute toxic effects.

METHODS

Chloroquine sulphate injection (May & Baker) containing 40 mg. base per ml. was used in most of the experiments; chloroquine phosphate injection (Bayer) containing 30 mg. base per ml. was used in a few experiments. All dosages mentioned below are in terms of the base. The solutions used were neutral to litmus.

Adult mongrel dogs and albino rats of either sex were administered increasing quantities of chloroquine. The acute toxic effects and fatality in 24 hours were recorded.

Twenty adult mongrel dogs of either sex (7-16 kg.) anaesthetized with phenobarbitone sodium (150 mg. per kg. i. p.) or pentobarbitone sodium (40 mg. per kg. i. p.) or Dial (0.6 ml. per kg. i. v.) or chloralose (100 mg. per kg. i. v.) were used for preliminary pharmacological studies. The trachea was cannulated and respiratory excursions were recorded with a Marey's tambour,

1. Present address: Department of Pharmacology, All India Institute of Medical Sciences, New Delhi.
2. Present address: Department of Pharmacology, T. N. Medical College, Bombay 8.

artificial respiration being given when necessary. Carotid blood pressure was recorded with a mercury manometer. Drugs were administered through the femoral vein. Splenic and intestinal volumes were recorded in two animals. Effects of various drugs, administered before or after chloroquine on the latter's actions were also studied in these experiments.

In 7 dogs anaesthetized with pentobarbitone sodium, electrocardiographic records from lead II were obtained before and after varying doses of chloroquine given intramuscularly or intravenously. Similar records were obtained in 5 dogs after chloralose anaesthesia, in 1 after Dial anaesthesia and in 2 after morphine sedation.

In 44 experiments chloroquine (1 to 3 mg. per kg.) was injected at different sites in the vascular tree in dogs anaesthetized with pentobarbitone sodium, the blood pressure being recorded from the femoral artery. The drug was injected into either femoral artery, either femoral vein, into both common carotid arteries and the left ventricle, the effect of each being noted. For injection into the left ventricle, the chest and pericardium were opened under artificial respiration. The injection time was less than one second and the time course of subsequent effects was recorded with a stop watch with accuracy of 1 second. Bilateral vagotomy and carotid denervation were also carried out in some of these experiments.

In 10 frogs the heart was perfused with frog Ringer through the vena cava after cutting the aorta. Effects of various dilutions of chloroquine on force and frequency of the heart beats were recorded.

Following the method of Burn (1952), for rats 5 hind limb preparations of frogs were perfused with frog Ringer and the effects of chloroquine and other vasoactive drugs on hind limb vessels were studied.

RESULTS

The mortality rate in dogs and rats following varying doses of chloroquine is shown in Table I. The gross toxic effects in dogs consisted of restlessness, dyspnoea, rigors, micturition and defaecation, gasping, convulsions and death. Convulsions were also noted in rats.

Fall of blood pressure was the most outstanding pharmacological effect of parenteral chloroquine in anaesthetized dogs (Fig. 1). Prolonged hypotension was accompanied by irregular respiration. Artificial respiration raised the blood pressure to some extent. The fall was detectable after 0.5 mg. per kg. i.v. and the blood pressure returned to normal in a few minutes. The extent and duration of the hypotension increased with the dose of the drug, relatively larger amounts being required by the intramuscular route than the intraven-

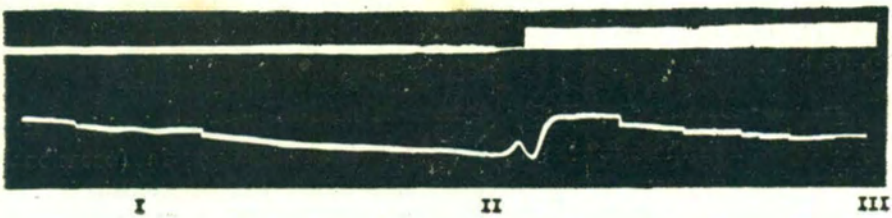

Fig. 1.

ous route. There was apparently no difference in the responses to chloroquine sulphate and phosphate. Splenic volume decreased slightly but intestinal volume was unaffected. After large doses (over 15-20 mg. per kg.) death usually occurred in 2 hours.

TABLE I

Mortality in rats and dogs after intramuscular chloroquine

Rats			Dogs		
Dose (mg./kg.)	No. of animals	Percentage mortality	Dose (mg/kg.)	Numher of animals	Percentage mortality
40	9	0	5	6	0
60	5	0	6	8	0
80	10	50	7	9	33
100	10	100	8	5	20
			9	7	29
			10	12	42
			12.5	6	83

Atropine (1 mg. per kg. i.v.) administered prior to chloroquine in 5 animals and phenergan (5 mg. per kg. i.v.) in 3 animals did not modify the response to chloroquine (0.5—10 mg. per kg. i.v.). Hydrocortisone (250 mg. in 250 ml. 0.9% saline i.v.) administered 2 hours prior to chloroquine (10 mg. per kg. i.v.) and cortisone acetate (75 mg. i.m.) administered 2 days prior to the experiment followed by 25 mg. 4 hours before chloroquine (10 mg. per kg. i.m.) also failed to modify the drug's effects.

Adrenaline (0.1 mg. intravenous or intracardiac) temporarily raised the blood pressure to normal levels after chloroquine (10 mg. per kg. i.v.) in 3 animals.

Early electrocardiographic changes were usually characterised by flattening or reversal in the direction of T waves. Sinus tachycardia (occasionally bradycardia), supraventricular rhythms, conduction blocks, ventricular premature beats, ventricular tachycardia, ventricular fibrillation and cardiac arrest were all noted (Fig. 2).

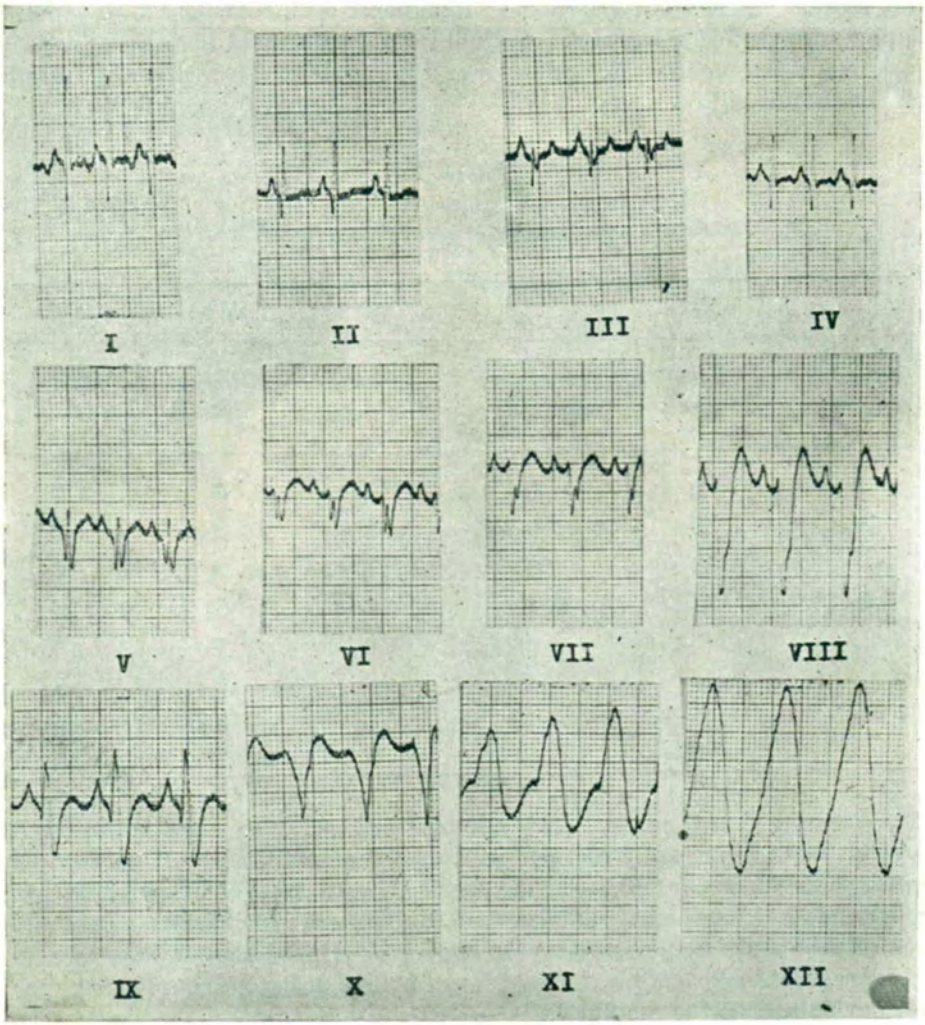

Fig. 2.

The latent periods of fall of blood pressure after injecting chloroquine into different parts of the cardiovascular tree are given in Table II. Vagotomy and carotid denervation did not affect the latent period or degree of the hypotension.

In the isolated frog heart, chloroquine in all the concentrations used (1 in 10^{-5} to 2 in 10^{-3}) decreased the amplitude and sometimes the frequency of contractions, higher doses eliciting an effect more quickly. With higher concentrations the heart beat irregularly, usually stopping in diastole.

TABLE II

Latent periods of fall of blood pressure after chloroquine (1-3 mg./kg.) injected by various routes

Route of administration	Number of dogs	Total number of injections	Latent period of fall of blood pressure in secs. (average and range)	Denervation	Latent period of fall of blood pressure after denervation in secs. (average and range)
Femoral artery..	3	6	22 (20–36)	–	–
Femoral vein ...	6	10	15 (12–19)	–	–
Common carotid arteries ..	8	15	11 (8–12)	Bilateral vagotomy (6 dogs)	10 (7–12)
				Bilateral carotid denervation (2 dogs)	11
Left ventricle ..	6	13	6 (4–6)	Bilateral vagotomy (3 dogs)	5 (4–6)

There was no evidence of vasodilation by chloroquine (1 to 5 mg. injected in perfusion tubing) in the perfused frog hind limb which responded as usual to adrenaline and sodium nitrite.

DISCUSSION

In anaesthetized dogs hypotension followed by respiratory disturbances were the outstanding effects noted in our initial experiments with chloroquine. The hypotension was not modified by atropine, phenergan, cortisone, vagotomy and carotid denervation and was only partially counteracted by artificial respiration.

Observations on the electrocardiogram of chloroquine treated dogs as well as those on the perfused frog heart and the perfused frog hind limbs

also suggest myocardial disturbances as the cause of the hypotension produced by chloroquine.

Injecting chloroquine in the left ventricle of the anaesthetized dog produced hypotension within the shortest period as compared to any other route of administration. This suggested a cardiac origin for chloroquine-induced hypotension since there is evidence that drugs injected in the left ventricular cavity have the most rapid access to the coronary circulation (Comroe, 1939).

Hess and Schmidt (1959) noticed reduction in contractile force in dog's heart after 2 mg. per kg. of chloroquine. Arora and Amrit Lall (1960) noted fall of cardiac output in dog heart lung preparation after adding 90 mg. chloroquine to the blood. LeComte (1955) noted hypotension in cats (under Dial anaesthesia) following chloroquine after vagotomy and treatment with an antihistaminic. Arora (1955) noted marked hypotension in cats and dogs after intravenous chloroquine. In all these reports hypotension appears to be due to cardiac toxicity of the drug. On the heart, chloroquine possesses antiarrhythmic (Arora, Sharma and Madan, 1955), negative inotropic, anticholinergic and vagolytic (Agarwal and Arora, 1956) and antiaccelerator (Arora and Amrit Lall, 1960) properties.

The clinical literature contains several references to hypotensive and myocardial toxic actions of chloroqui .e. Scott (1950) noticed fall of blood pressure (mainly systolic) in adults receiving on an average 8 mg. per kg. chloroquine intravenously. The degree of hypotension and severity of other symptoms were directly proportional to the rate of injection and concentration of chloroquine used, as would be expected in a drug showing high tissue affinity. Changes in pulse rates in this series were too insignificant to explain the hypotension. Wilkinson (1953) who gave chloroquine orally for amoebic hepatitis (upto 0.9 gm. per day in adults) noted hypotension and E. C. G. changes amongst several other toxic effects. Alving (1948) reported reversible flattening and depression of T waves in E. C. G. records during chronic chloroquine administration to volunteers. Sanghavi (1956) observed serious reactions after chloroquine (8—12 mg. per kg. i. v.) in 4 patients suffering from atrial fibrillation. The E. C. G. changes in his patients are comparable to those described above in dogs. Harris (1955, 1957) reported sudden death in 3 infants after intramuscular chloroquine and suggested sudden hypotension as the cause of death. Kjaer (1955) reported acute accidental poisoning with chloroquine in a pregnant woman; fainting (attributed to central nervous toxicity) was one of the symptoms noted but pulse rate, blood pressure and E. C. G. changes were not reported. Hobbs, Sorsby and Freedman (1959) suggested vascular spasm as the cause of retinopathy in 3 patients after chronic chloroquine therapy.

The possibility of "collapse" in children after intramuscular chloroquine in quantities exceeding 5 mg. per kg. is mentioned in the literature. The recommended adult dose is 400 mg. (6—7 mg. per kg.). Comparison of the reports by Sanghavi (1956) and Harris (1955, 1957) does not indicate greater susceptibility of infants. The possibility of myocardial disturbances and hypotension should therefore always be borne in mind whenever chloroquine is used parenterally especially in view of the low toxic dose noted in animal.

In anaesthetized dogs intravenous or intracardiac injection of adrenaline (0.1 mg.) following chloroquine could always raise the blood pressure, though for a short period. In desperate collapse after parenteral chloroquine in clinical practice, single or repeated intracardiac injections of adrenaline may be of resuscitative value.

SUMMARY

(1) Acute toxic effects of parenterally administered chloroquine were studied in animals.

(2) The main findings were hypotension followed by respiratory disturbances in dogs. Hypotension was mainly due to myocardial depression as borne out by studies on the dog E. C. G., the latent period of the hypotension following injection of the drug at various sites, perfused frog heart and perfused frog hind limb.

(3) The literature on the acute pharmacological effects and clinical toxicity of chloroquine is reviewed and the risks accompanying its parenteral use emphasised.

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