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Chloroquine Drug Interactions Part II – Interaction with Diuretics

A.N. GUANTAI[1]*, I. ADDAE-MENSAH[2], D. K. NJOROGE[1], R. W. MUNENGE[1]

[1]*Department of Pharmacology and Pharmacognosy, Faculty of Pharmacy, University of Nairobi, P.O. Box 19676, Nairobi.*
[2]*Chemistry Department, University of Ghana, P.O. Box 25, Legon.*

Chloroquine, a commonly used antimalarial agent was investigated for interaction with common diuretics, furosemide and chlorthiazide. Examination of urine samples collected from water loaded rats at hourly intervals revealed that chloroquine antagonized the furosemide and chlorthiazide induced diuresis. It also decreased the natriuretic and enhanced the kaliuretic effects of furosemide and chlorthiazide.

Key Words: Chloroquine, furosemide, chlorthiazide, drug interaction, diuretics, kaliuresis, natriuresis.

INTRODUCTION

Malaria is a disease that has no age, sex, ethnic or socio-economic boundaries. Originally, the disease was limited to the warm humid tropical regions, but with the advancement of technology and improved methods of travel, incidences of "imported malaria" [1,2] have steadily increased and hence the disease has now become a global problem prompting the World Health Organization to step up its campaign on malaria vector control and chemotherapeutic management of the disease [3].

Except for haemoglobinopathies such as sickle cell anaemia, thalassaemia and in erythrocyte metabolic disorders such as glucose-6-phosphate dehydrogenase enzyme deficiency where a degree of resistance to malaria is conferred [4], most if not all the other disease conditions, chronic or otherwise, may occur in association with malaria and multiple drug therapy is consequently indicated. Thus, clinical or experimental experience is necessary because interaction between the antimalarial agent and other drugs might be of practical importance. The antimalarial agent chloroquine (CQ), a 4-aminoquinoline is used in the management of suspected or confirmed cases of malaria in Kenya [5] and generally in the tropics [6]. The drug is indicated in the treatment and prophylaxis of malaria in areas where there is no chloroquine resistance or only R1 type resistance is present [7].

In Kenya, chloroquine used to be available not only on prescription but also sold as an over-the-counter item in pharmacies, supermarkets and in ordinary small shops ("kiosks") for use in self medication [8]. Due to this wide and unrestricted availability, the drug was liable to misuse by the ill-informed and also to abuse by ill-intentioned persons [8]. Currently, in Kenya the drug is available as a prescription only medicine [9].

Although chloroquine has been promoted as a well tolerated drug with mild adverse effects when used in therapeutic doses [7], literature on its interactions with other drugs especially those used in management of chronic disease conditions is scanty and sometimes totally lacking. The present study describes the interaction of chloroquine with furosemide (F) and chlorthiazide (CTZ) diuretics that are commonly used in management of acute and chronic oedematous conditions with or without complications.

MATERIALS AND METHODS

Materials – Materials and reagents used were sourced as follows. Chloroquine phosphate (ET Monks, Nairobi, Kenya), furosemide (Hoechst, Germany), chlorthiazide (Merck Sharp and Dohme), potassium chloride (Sigma), sodium chloride, (BDH Ltd., Poole, England) flame photometer and potassium/sodium ion filter cells (Corning Eel Scientific Instruments).

* Author to whom correspondence may be addressed.

Treatment of Animals

Thirty Wistar rats of both sexes bred under experimental conditions were fasted for 24 hours. They were then weighed individually and loaded by stomach tube with warm water at 5 ml/100g body weight. The animals were then divided into six groups of five, put in metabolic cages and left for 40-60 minutes after which they were orally fed as follows:

Control (GR1) - normal saline 1ml/kg body weight.
CQ (GR2) - chloroquine phosphate 50 mg/kg body weight.
CQ/CTZ (GR3) - chloroquine phosphate 50 mg/kg and chlorthiazide 35 mg/kg body weight.
CTZ (GR4) - chlorthiazide 35mg/kg body weight.
CQ/F (GR5) - furosemide 20 mg/kg and chloroquine phosphate 50 mg/kg body weight.
F (GR6) - furosemide 20 mg/kg body weight.

All drugs were administered in the same volume of saline as the control.

Collection of urine samples

Samples of urine were collected from each of rats at one-hour interval for a total of 4 The hourly samples were kept separately.

Preparation of standard curves for Potassium and Sodium ions

Standard solutions of potassium and sodium ions were separately prepared using analytical grade potassium chloride and sodium chloride. Serial dilutions were subsequently made using distilled de-ionized water and the respective ionization intensities of these solutions determined using potassium and sodium ion filter cells fitted into a flame photometer. The data obtained was used to draw standard calibration curves of ion concentration versus ionization intensities.

Urinalysis

In order to assess the urinary sodium and potassium excretion, urine samples were diluted appropriately and the ionization intensities of resulting solutions determined as described above for the standard solutions. Using the standard calibration curves, the corresponding potassium and sodium ion concentrations of the diluted urine samples were read off and the urinary ion concentration in the undiluted urine obtained by multiplying the calibration curve reading with the urine dilution factor.

RESULTS

Table 1 and 2 reflect the hourly changes in sodium and potassium excretion, whereas table 3 shows the cummulative effect on diuresis, natriuresis and kalliuresis. The results show that chloroquine decreased the furosemide and the chlorthiazide-induced diuresis. On electrolyte excretion, chloroquine exhibited relatively mild natriuretic (82.4%) effect whereas furosemide and chlorthiazide caused 337.7% and 281.3% sodium loss, respectively, with respect to the control group values (table 3).

Concurrent administration of chloroquine with furosemide or chlorthiazide led to a decrease in the natriuretic properties of these diuretics. There was 182.5% and 84.5% cummulative decrease in the sodium losing activity of furosemide and chlorthiazide, respectively, after 4 hours with respect to control group (table 3).

With regard to potassium excretion, chloroquine caused an increase in potassium loss (43.4%). Furosemide and chlorthiazide recorded 54.2% and 75.4% potassium loss, respectively, after 4 hours with respect to control group.

Concurrent administration of chloroquine with furosemide or chlorthiazide led to potentiation of the kaliuretic effect of the two diuretics registering 86.8% and 81.5%, respectively.

Table 1: Modification of chlorthiazide and furosemide induced natriuresis by chloroquine with time and with respect to zero time sample

	Mean percentage change in Sodium loss with time					
Time (Hrs)	Control GR1	CQ GR2	CQ/CTZ GR3	CTZ GR4	CQ/F GR5	F GR6
0	0.0	0.0	0.0	0.0	0.0	0.0
1	4.5	54.4	88.9	191.2	114.1	144.1
2	-21.5	54.4	73.3	197.2	103.4	191.7
3	4.5	45.1	132.3	256.8	107.9	186.8
4	2.0	72.7	248.1	291.2	34.8	278.5

Table 2: Modification of chlorthiazine and furosemide induced kaliuresis by chloroquine with time and with respect to zero time sample

	Mean hourly percentage change in potassium loss with time					
Time (Hrs)	Control GR1	CQ GR2	CQ/CTZ GR3	CTZ GR4	CQ/F GR5	F GR6
0	0.0	0.0	0.0	0.0	0.0	0.0
1	18.1	33.6	33.3	71.2	48.3	68.6
2	-3.2	17.4	22.1	55.5	56.9	47.4
3	4.6	30.0	71.0	62.2	104.8	39.6
4	8.2	38.3	95.0	76.3	113.7	33.2

Table 3 Cumulative effect of chloroquine on the diuretic, natriuretic and kaliuretic effect of furosemide and chlorthiazide in rats after 4 hours

Effect	Mean percentage change with respect to control (GR1)					
	CONTROL GR1	CQ GR2	CQ/CTZ GR3	CTZ GR4	CQ/F GR5	F GR6
Diuretic	0.0	14.9	20.0	29.2	40.2	56.3
Natriuretic	0.0	82.4	196.8	281.3	155.2	337.7
Kaliuretic	0.00	43.4	81.5	75.4	86.8	54.2

DISCUSSION

Evidence from the present study shows that chloroquine may adversely interact with furosemide and chlorthiazide which are some of the commonly prescribed diuretics in the management of oedematous disease conditions such as hypertension, congestive cardiac failure, hepatic oedema. The drug antagonized the diuretic and natriuretic, but enhanced the kaliuretic properties of furosemide and chlorthiazide (table 3).

The decreased urine output noted during diuretic/chloroquine combination therapy was probably a consequence of the enhanced sodium retention (table 1 and 3) considering that sodium is the main extracellular cation associated with oedematous conditions, and that, facilitation of its urinary loss is an essential property of an effective diuretic. It therefore follows that the antidiuresis induced by chloroquine-diuretic combination may be a major drawback to the diuretic effectiveness of furosemide and chlorthiazide.

The greatest antagonism was observed with furosemide whereby the loss of sodium was reduced from 337.7 % for furosemide to 155.2% furosemide/chloroquine with respect to untreated control within four hours. In case of chlorthiazide and chlorthiazide-chloroquine combination, the figures stood at 281.3 and 196.8% respectively. (table 3). This represents 182.5% reduction in the natriuretic effectiveness of furosemide and 84%

for chlorthiazide respectively. It is therefore possible that the main site of action of chloroquine in the kidneys is at the loop of Henle and distal segment where furosemide is known to act, not overlooking a generalized effect in probably the whole of nephron.

In addition, the antidiuretic action of chloroquine could also be due to its inhibition of prostaglandin synthesis and release [10, 11], which have been advocated as the possible mechanism of the anti-rheumatic action of the drug [11, 12]. Other anti-inflammatory drugs e.g. the non-steroidal group possess prostaglandin synthesis and release inhibitory effects and their antidiuretic effect has been attributed to the inhibition of renal prostaglandin E [13].

Hypokalaemia is one of the major side effects associated with the use of potent diuretics such as the loop diuretics (furosemide) and thiazide diuretics (chlorthiazide). Results of the present study have confirmed the potassium depleting effects of furosemide and chlorthiazide, and most important they have demonstrated the potentiation of the kaliuretic properties of furosemide and chlorthiazide by chloroquine.

Drug induced hypokalaemia can be a major problem especially in patients with chronic obstructive pulmonary disease since hypo-kalaemia may exacerbate metabolic alkalosis and worsen the hypoventilation in patients with chronic carbon dioxide retention [7]. Other risk groups are those of patients with severe heart disease, those on digoxin, those with severe liver disease or with severe skeletal muscle contractile disorders.

In these cases, potassium supplementation is necessary especially if the serum potassium concentration falls below 3.0 mmol/litre. This illustrates the major role of potassium in the body's physiological functions and emphasizes the clinical significance of the chloroquine/diuretic interaction demonstrated in this study.

Although these observations were made in animals, they should indicate caution during the use of chloroquine-diuretic combination therapy.

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