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EFFECT OF ORAL AMODIAQUINE ADMINISTRATION ON SOME HOMEOSTATIC VARIABLES IN HEALTHY NIGERIANS

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ABSTRACT: The effects of oral amodiaquine (aq) on blood glucose, blood pressure and urinary electrolytes were investigated in six healthy male young adults. Amodiaquine caused a fall in blood pressure without hypotensive features and a fall in blood glucose without hypoglycaemic symptoms. There were no disturbances in electrolyte balance. Amodiaquine may therefore be used in dehydrated patients without the fear of worsening electrolyte balance in such patients.

Key Words: Chloroquine; Amodiaquine; Malaria; Blood glucose; Blood pressure; Electrolyte balance.

INTRODUCTION

Chloroquine is more widely used in the treatment of uncomplicated malaria than amodiaquine. This is probably due to the greater degree of toxic effects of amodiaquine, which is more effective than chloroquine in clearing parasitaemia in drug resistant falciparum malaria (1,2). Nausea and pruritus have been demonstrated more frequently in patients treated with chloroquine than those treated with amodiaquine (3) and these unwanted side effects have discouraged some patients from using chloroquine. It has, however, been suggested that there might be no advantage of amodiaquine in the treatment of patients with *Plasmodium falciparum* infection in chloroquine resistant areas.

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Furthermore, there might be development of cross resistance in *P. falciparum* to the 4-aminoquinolines which is complete and parallel (4). It has been established that amodiaquine is more toxic than chloroquine, having been associated with hepatitis and agranulocytosis with myelotoxicity in humans (5). It has been difficult to make a choice between these two 4-aminoquinolines in the treatment of uncomplicated malaria.

Natriuresis has been reported to follow acute administration of chloroquine in rats (6) and it is not certain if the structurally related amodiaquine would exhibit this property, which may increase the degree of toxicity of the drug and thus limit its usefulness. It is not however known if disturbances in blood pressure and

glucose homeostasis would follow the use of these anti-malarials.

The aim of this study was therefore to determine the possible effects of amodiaquine on electrolyte balance, glucose homeostasis and blood pressure effects in healthy subjects. This will be a pointer to the rationale use of amodiaquine in patients with malarial, especially when other homeostatic considerations are important to the patients' management.

SUBJECTS AND METHODS

Six male Pharmacy students of the University of Ibadan were recruited for the study after responding to an informal advertisement during a lecture in pharmaceutical chemistry. They were aged between 20 and 24 years. Three other male subjects aged 20 - 22 years were also recruited to serve as controls. None of the subjects was on any regular medication and none had taken any form of antimalarials three months prior to the study. None of them had clinical or laboratory features of malaria during the study, which spanned a period of two days. Presently evaluation of the subjects was performed to ascertain their health status. Such tests included blood film for malaria parasites, serum electrolyte and urea and blood pressure measurement. They were all normal.

Two tablets of amodiaquine (Parke-Davis & Co., Detroit, U.S.A), equivalent to 400mg base, USP, were swallowed wholeby each of the subjects with 400ml of distilled and deionised water on the morning of the second day of the study, after an overnight fast. A light break-fast was allowed, 4hr after the drug administration. The three control subjects did not take amodiaquine but drank 400ml of distilled and deionised water. Their breakfast was also delayed for 4 hr to correspond to the timing for the test subjects. Subsequently, water was allowed ad libtium and no dietary in a fasting state, however, on the morning of the third day for the final determination of their variables.

Blood samples were collected from finger prick, by the use of sterile lancet, onto the test strip of a Check-Mate blood glucose meter (Cascade Medical Inc., Minn. USA) for blood glucose determination. The blood samples were obtained immediately before drug administration (time 0) and ½, 1, 2, 4 and 24 hr after drug administration.

24 hr urine samples were collected by a standard procedure understood by all participants. On day 1 of the study, each subject was instructed to empty his bladder at 7.00 a.m. and thereafter to collect all urine voided into a plastic keg containing 5ml 0.1M H_2SO_4 as preservative, until 7.00 a.m. on the second day. Another 24 hr urine sample was similarly collected for the second 24 hr period of the study following amodiaquine administration. The volume of each 24 hr urine was carefully measured and aliquots of 10ml each were collected into universal transported frozen to the Chemical Pathology Laboratory of the Ogun State University Teaching Hospital, Sagamu, for the analysis of glucose and electrolytes.

Urine glucose was determined by the method described by Ceriotti (7). Urine sodium and potassium were determined by flame emission spectrometric, and chloride by titrimetric methods (8).

Blood pressure was measured with an Accoson sphygmomanometer just before blood samples were obtained. The fifth phase of Koroktoff sound was taken as the diastolic pressure. The mean arterial blood pressure (MAP) was calculated by adding one third of the pulse pressure to the diastolic pressure. The pulse pressure is the difference between the systolic and diastolic measures of the blood pressure.

Statistical Analysis:

The values of all variables are presented as mean ± standard deviation. Statistical analysis was performed using Students' t-test to compare the mean values of urinary variables before and after drug administration in the test subjects; and blood sugar values in test subjects and control subjects. Significance levels were checked for in standard statistical tables using 95% confidence limits.

Table 1: Urinary electrolytes and glucose concentrations before and after amodiaquine administration.

	Before	After	P-value
Volume of urine (ml)	991.70 ± 82.50	960.80 ± 38.21	0.30
Glucose (mg/ml)	8.17 ± 3.66	4.00 ± 2.68	0.04
Sodium mmol/L)	89.17 ± 49.84	65.00 ± 31.30	0.28
Potassium (mmol/L)	22.42 ± 9.78	16.58 ± 14.63	0.26
Chloride (mmol/L)	74.67 ± 42.48	45.33 ± 25.33	0.08

Values represent the means ± S.D.

RESULTS

Two subjects complained of mild abdominal discomfort and five of dizziness after about 3 hr following the administration of amodiaquine. All the six test subjects complained of a slight headache. They were all relieved of these complaints without any medical treatment. None of the control subjects had any of such complaints.

There was no significant difference in the volume of 24 hr urine prior to, and following amodiaquine administration, the volumes being 991.70 ± 82.50 ml and 960.80 ± 38.21 ml before and after drug administration. 24 hr urinary excretion of glucose, sodium, potassium and chloride decreased following amodiaquine administration. None of these changes, except that for glucose was, however, significant (Table 1).

Figure 1 shows that amodiaquine causes a decrease in blood glucose level. The decrease became apparent two hours after drug administration and at 4 hr, there was an even greater fall in blood glucose. Twenty four hours after amodiaquine administration, blood glucose level had risen but it was still slightly less than the value before drug administration.

The mean arterial blood pressure also decreased to a significant level 2 hr after amodiaquine administration. The value was still significantly lower 4 hr after drug administration. The blood pressure had risen to the pre-drug administration level by 24 hr after amodiaquine administration (Fig. 2).

DISCUSSION

The self limiting side-effects experienced by most of the subjects may be due to the fasting state at which time the subjects took the drug. Usually chloroquine and amodiaquine are advised to be taken after eating. Absorption of amodiaquine taken by these subjects would probably be rapid and blood level of amodiaquine would be higher than it would have been if taken with food. The side-effects could also be a manifestation of the fall in blood sugar and blood pressure following amodiaquine administration. None of the subjects had malaria at the time of drug ingestion and so it is possible that the reported side-effects would not be present when patients take amodiaquine for therapeutic purposes. In the first place, there would be malaria parasites to clear and secondly the drug would be administered with food.

There has been a report of fall in the arterial blood pressure of rats after oral chloroquine administration (9) and in humans after intravenous chloroquine infusion (10). The fall in the blood pressure observed in this study was not, however, enough to give rise to hypotensive symptoms and it can be assumed safe to take amodiaquine into empty stomach without adverse side-effects.

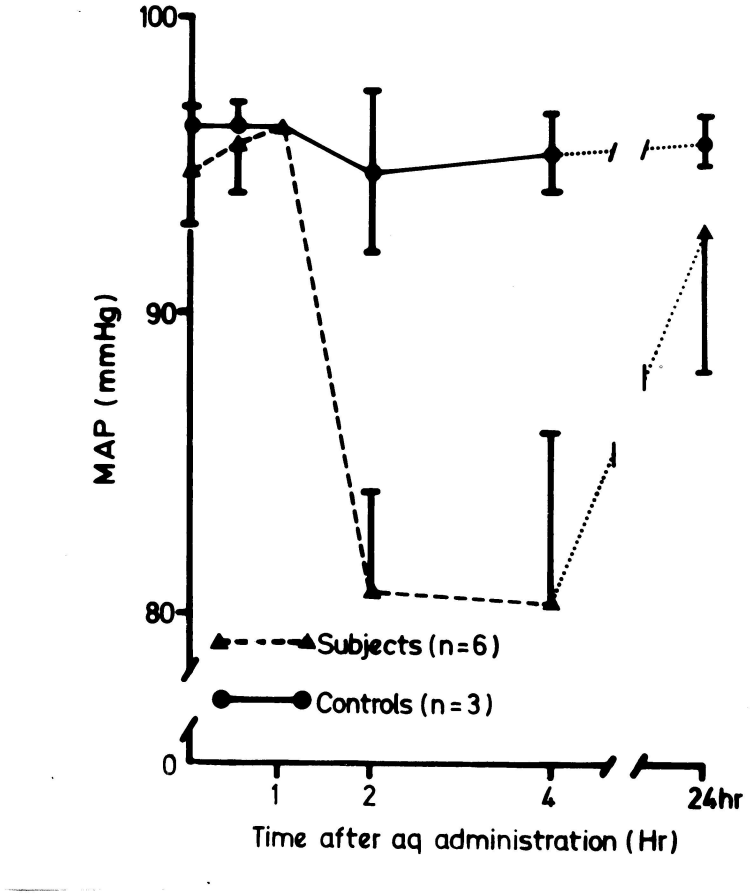

Fig. 1: Effect of Amodiaquine Administration on Mean Arterial Blood Pressure

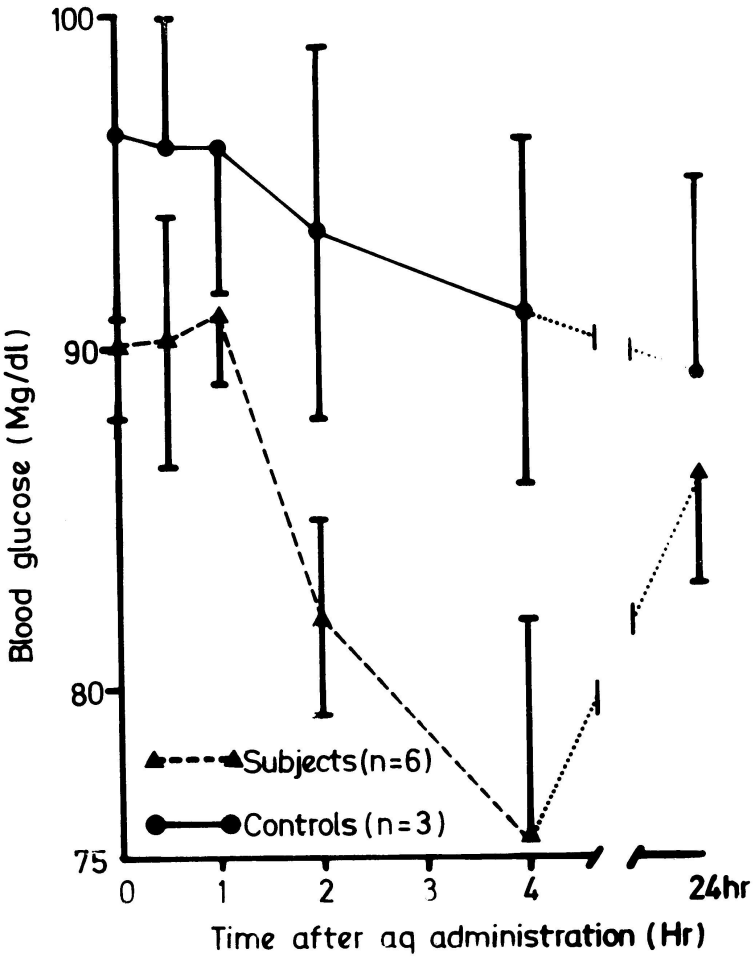

Fig. 2: Effect of Amodiaquine Administration on Blood Glucose Level.

The fall in blood sugar following amodiaquine ingestion, even though significant, was not associated with hypoglycaemic symptoms. The mechanism by which amodiaquine administration causes a fall in blood sugar level is not immediately apparent from this study. The decreased excretion of sugar in the urine occasioned by amodiaquine intake makes it difficult to implicate altered renal handling of sugar as a possible mechanism. The fasting state of the subjects might partly be contributory to this but it would not explain this degree of fall in blood sugar. The control subjects, who were similarly fasting, did not have a lowering of blood sugar level. It is also possible that a meal at the time of drug intake could have abolished the amodiaquine-induced fall in blood sugar level. There were no facilities to measure plasma insulin level, as this would have thrown light to the role of amodiaquine in influencing insulin release. The only plausible guess that can be inferred from this study may have something to do with an increase in plasma insulin level, stimulated by amodiaquine administration. It would have also been interesting to see if i fection by plasmodium would make any difference to this degree of fall in blood sugar level following intake of amodiaquine.

Urinary electrolyte excretion was not affected by amodiaquine intake. Plasma electrolyte concentrations were not determined and so it is difficult to comment on electrolyte balance. Serious electrolyte disturbance would have been reflected in the urinary loss of the electrolytes.

In conclusion, oral administration of amodiaquine in normal subjects causes only a slight fall in blood pressure and in blood glucose level without any electrolyte disturbance. Amodiaquine may then be used safely in patients with malaria who are dehydrated, as there can be no fear of worsening of any electrolyte derangement which may be present in such patients.

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REFERENCES

1. Looareesuwan, S.; Phillips, R.S.; White, N.J.; Karbwang, J.; Benjassurat, Y.; Attanath, P. and Warrell, D.A. (1995). Intravenous amodiaquine and oral amodiaquine-erythromycin in the treatment of chloroquine resistant falciparum malaria. Lancet; ii: 805 - 808.
2. Salako, L.A. and Aderounmu, A.F. (1987). In vitro chloroquine and mefloquine-resistant *P. falciparum* in Nigeria. Lancet; i: 572 - 573.
3. Brasseur, P.; Agnamey, P.; Ekobo, A.S.; Samba, G.; Favennec, I. and Kouamouo, J. (1995). Sensitivity of *Plasmodium falciparum* to amodiaquine and chloroquine in Central Africa: a comparative study in vivo and in vitro. Trans. R. Soc. Trop. Med. Hyg.; 89: 528 - 530.
4. Misra, S.P.; Nandi, J. and Lai, S. (1995). Chloroquine versus amodiaquine in the treatment of plasmodium malaria in North East India. Indian J. Med. Res. ; 102: 119 - 123.
5. Tingle, M.D.; Jewell, H.; maggs, J.L.; O'Neill, P.M. and Park, B.K. (1995). the bioactivation of amodiaquine by human polymorphonuclear leucocytes in vitro: chemical mechanisms and the effects of fluorine substitution. Biochem. Pharmacol.; 50: 1113 - 1119.
6. Musabayane, C.T.; Ndhlovu, C.E.; Mamutse, G.; Bwititi, P. and Balment, R.J. (1993). Acute chloroquine administration increases renal sodium excretion. J. Trop. Med. Hyg.; 96: 305 - 310.
7. Ceriotti,, G. (1971). Blood glucose determination without deproteinization, with use of o-toluidine in dilute acetic acid. Clin. Chem.; 17: 201.
8. Christian, G. D. (1980). Mercurimetric determination of blood or urine chloride and flame emission spectrometric determination of sodium. In: Analytical Chemistry, 3rd Ed. John Wiley and Sons, New York. pp. 241 - 243 and 434 - 435.
9. Sofola, O. A.; Olude, I.O. and Adegoke, F. (1981). The effects of chloroquine toxicity on blood pressure in rats. J. Trop. Hyg. 84: 249 - 252.
10. Aviado, D.M. and Bellet, S. (1969). Comparative toxicity of chloroquine [(chloro-7"-quinoly-4"-)-amino-2'-propyl] 1,4-piperazine (WR 3683). Toxicology and Applied Pharmacology; 15: 331 - 344.