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Effects of the Leaf Extract of *Telfairia occidentalis* on the Pharmacokinetics of Chloroquine in Rats

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Abstract: Effects of ethanol leaf extract of *Telfairia occidentalis* on the pharmacokinetics of chloroquine were evaluated. Seventy five Wistar albino rats were divided into three equal groups. Chloroquine only (10 mg kg⁻¹) was administered orally to group A. While group B received chloroquine (10 mg kg⁻¹) 1 h after the leaf extract of *T. occidentalis* (250 mg kg⁻¹) orally. Chloroquine (10 mg kg⁻¹) and the extract were simultaneously co-administered orally to group C. Blood samples were collected through cardiac puncture from the rats at 0.25, 0.5, 1.0, 2.0 and 5.0 hours after chloroquine administration. Serum was obtained from the blood sample by centrifugation. Chloroquine concentration in the serum was determined using ultraviolet (UV) Spectrophotometer. Results obtained showed that the co-administration of the extract both one hour before and simultaneously with chloroquine significantly (p<0.05) elevated the values of some pharmacokinetic parameters. Administration of the extract one hour before chloroquine increased Ke (0.0830), Ka (3.7275), A (119.4706), C_{max} (107.0334) and t₀ (0.0873), while simultaneous co-administration of the extract and chloroquine also increased these parameters Ke (0.2330), Ka (3.7806), A (149.4012), C_{max} (116.7488) and t₀ (0.0764) compared to chloroquine only (control) which has Ke (0.0552), Ka (2.6676), A (109.1809), C_{max} (107.0334) and t₀ (0.0873). Both cases also decreased t_{1/2} (8.3495 and 2.9742), Vd (367.2781 and 138.0328) and F (0.4290 and 0.1935) for the administration of extract one hour before chloroquine and simultaneous administration of extract and chloroquine, respectively, compared to control (chloroquine only): t_{1/2} (12.5544), Vd (544.7877) and F (0.5825). These results showed that co-administration of the leaf extract of *Telfairia occidentalis* both one hour before or simultaneously with chloroquine affect the pharmacokinetics of chloroquine, and may thereby render it ineffective.

Key words: Pharmacokinetics, *Telfairia occidentalis*, chloroquine

INTRODUCTION

Malaria is a huge public health problem in Africa that is responsible for more than one million deaths annually. In line with Roll Back malaria initiative and the Abuja Declaration, African countries have intensified their fight against malaria (Andrew *et al.*, 2006). For a long time now, chloroquine has been the first choice of antimalaria drug in some malaria endemic areas. Unfortunately, the issue of resistance by the malaria parasites to chloroquine has become a serious factor against the use of chloroquine.

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There are inconsistencies surrounding chloroquine resistance in vivo because of the modulatory influence of other biological, environmental and genetic factors such as variation in chloroquine uptake, distribution, metabolism and elimination (i.e. pharmacokinetics) in humans. Attention should therefore be given to biological and social factors like diet, nutritional status, inflammatory and infection processes that are often present in areas where malaria is endemic (Guzman and Jaime, 2006).

Some plant materials have been found to affect the pharmacokinetics of chloroquine. The concurrent oral administration of aqueous leaf extract of *Azadirachta indica* (Meliaceae) with chloroquine sulphate resulted in a significant decrease in serum concentration, slower absorption and elimination as well as longer half-life of chloroquine sulphate (Shannon *et al.*, 2006). Similarly, rabbits fed on normal feed with 25% Spinach diet had a peak delay of one hour following oral chloroquine administration. Spinach maintained high chloroquine blood level (Owoyale *et al.*, 1995).

Telfairia occidentalis popularly known as fluted pumpkin is widely cultivated in southern part of Nigeria mainly for its nutritional value (Akoroda, 1990; Okoli and Mgbeogu, 1983). However, its medicinal importance is gradually attracting the attention of researchers. It has been established that the plant is useful in the treatment or management of ailments such as anemia (Ajayi *et al.*, 2000), diabetes (Eseyin, 2000, 2005, 2007; Nwozo *et al.*, 2004; Aderlbigbe *et al.*, 1999). Since pharmacokinetics of Chloroquine is known to be affected by concomitant administration of some plant extracts, this study was undertaken to determine the effect of the leaf extract of *Telfairia occidentalis*, a very popular vegetable in Nigeria and some part of West Africa, on the pharmacokinetics of chloroquine.

MATERIALS AND METHODS

Plant Collection

The leaves of *Telfairia occidentalis* Hook F were obtained in November 2005 from the medicinal plant garden of the Faculty of Pharmacy, University of Uyo, Nigeria. Identification of the plant was done by Dr. K. Ajibesin, a pharmacognosist in the same faculty.

Extraction

The leaves were washed with tap water to remove traces of sand and then set aside for water to drain off. They were then chopped into smaller pieces. 3.388 kg of the leaves were macerated in 4.5 L of 96% ethanol for seven days at room temperature. The extract obtained was filtered and the solvent removed with the aid of a rotary evaporator. The residue obtained was dried in a desiccator containing silica gel.

Animals

Albino Wistar rats weighing 100.76 ± 20.86 g were obtained from the animal house of the pharmacology department of the University of Jos, Nigeria. The rats were housed in cages under standard condition of light (12 h light, 12 h dark), humidity and temperature in the animal house of the University of Uyo, under the care of experienced animal technicians. They were fed on growers palletized feed and water.

Animal handling conformed to the ethical standard of the Animals ethics committee of the Faculty of Pharmacy, University of Uyo, Nigeria.

Administration of Chloroquine and Extract

Seventy-five overnight fasted rats were divided into three equal groups: A, B and C. Group A which served as control was administered chloroquine (10 mg kg^{-1}) only. Group B received

Chloroquine (10 mg kg⁻¹) one hour after the leaf extract of *T. occidentalis* (250 mg kg⁻¹). Group C was given the extract (250 mg kg⁻¹) and chloroquine 10 mg kg⁻¹) simultaneously. All administration was done orally. Distilled water was used to prepare the solution of chloroquine and the extract.

Collection of Blood Samples

Blood samples were collected at 0.25, 0.50, 1.00, 2.00 and 5.00 h by cardiac puncture from the rats under chloroform anaesthesia (5 rats per time point).

Analysis of Blood Samples

The blood samples collected were centrifuged at 3000 rpm for 5 min to obtain blood serum. Chloroquine concentration in the serum was quantified using ultraviolet Spectrophotometer (Unicam 8625) at 344 nm. Blood serum of rats which were not treated with either the extract or chloroquine was used as blank.

Determination of Serum Chloroquine Concentration

The serum concentration of chloroquine was determined by extrapolation from a standard curve of chloroquine concentration versus absorbance (344 nm).

RESULTS AND DISCUSSION

The results obtained are displayed on Table 1 and 2. Administration of *Telfairia occidentalis* before chloroquine increased the values of Ke (0.0830), Ka (3.7275), A (199.4706), C_{max} (107.0334) and t₀ (0.0873) compared to chloroquine only (control): 0.0552, 2.6676, 109.1809, 98.5097 and 0.0645, respectively and also decreased t_{1/2} (8.3495), Vd (367.2781) and F (0.04290) compared to control (12.5544, 544.7877 and 0.5825, respectively). Simultaneous co-administration of extract of *T. occidentalis* and chloroquine increased the values of Ke (0.2330), B (105.5540), Ka (3.7806), A (149.4012), C_{max} (116.7488) and t₀ (0.0764), but reduced the values of t_{1/2} (2.9742), Vd (138.0328), F (0.1935) and t_{max} (0.7855).

These results show that the leaf extract of *T. occidentalis* either when administered one hour before or simultaneous with chloroquine increased the absorption rate (Ka), elimination rate (Ke), Hybrid constant of absorption (A), maximum concentration (C_{max}) and lag time (t₀) and also decreased half-time (t_{1/2}), apparent volume of distribution (Vd) and Bioavailability (F).

The enhanced absorption of chloroquine after an initial delay (lag time) may be due to the neutralization of the gastric acidity by the metallic ions present in the leaf (Fasuyi, 2006), since chloroquine which is a basic drug is more absorbed in basic than acidic medium (Anne *et al.*, 1989; Tolaniyi, 2000). Basification of the urine may also be one of the factors responsible for the enhanced rate of elimination of chloroquine. While simultaneous administration of extract with chloroquine increased absorption rate by 41.7%, administration of chloroquine 1 hour after extract increased absorption rate by 39.7%. The time taken for chloroquine to attain maximum concentration (C_{max})

Table 1: Serum concentration of chloroquine (mg mL⁻¹) at different times

Time (h)	Chloroquine only	<i>Telfaira occidentalis</i> 1 h before chloroquine	<i>Telfaira occidentalis</i> plus chloroquine (simultaneous)
0.25	22.9592±6.0510	31.0297±9.0909	40.5844±5.1918
0.50	64.3321±2.1293	71.0111±4.7378	60.8998±8.7447
1.00	78.3395±4.0605	77.9225±3.9500	77.0872±1.3728
2.00	71.8002±9.6045	67.3470±6.1927	66.1890±5.9869
5.00	70.9907±0.4822	69.8980±1.9381	63.0798±7.0789

Mean±SD

Table 2: Pharmacokinetic parameters of chloroquine (10 mg kg⁻¹) after a single dose administration of 250 mg kg⁻¹ *Telfairia occidentalis* leaves

Parameters	AUC (Ug h mL ⁻¹)	Ke (h)	B (Ug mL ⁻¹)	Ka (h)	A (Ug mL ⁻¹)	T _{1/2} (h)
Chloroquine only (control)	334.3352±24.3079	0.0552±0.0001	80.1911±0.0227	2.6676±0.0001	109.1809±0.0332	12.5544±0.0322
Telfairia occidentalis 1 h before chloroquine	328.4906±12.2524	0.0830±0.0002*	79.4679±0.0318*	3.7275±0.0002*	119.4706±0.0060*	8.3495±0.0201*
Telfairia occidentalis plus chloroquine simultaneously	312.7202±22.9641	0.2330±0.0001*	105.5540±0.0299*	3.7806±0.0001*	149.4012±0.0044*	2.9742±0.0018*

Parameters	Vd (mL kg ⁻¹)	Cl (mL h ⁻¹)	F	C _{max} (Ug mL ⁻¹)	T _{max} (h)	T _r (h)
Chloroquine only (control)	544.7877 40.4561	30.0772±2.3028	0.5825±0.0432	98.5097±0.0180	1.4844±0.0009	0.0645±0.0001
Telfairia occidentalis 1h before chloroquine	367.2781±13.4638*	30.4863±1.1820	0.4290±0.0158*	107.0334±0.1765*	1.0440±0.0007*	0.0873±0.0021*
Telfairia occidentalis plus chloroquine simultaneously	138.0328 10.7864*	32.1616±2.5137	0.1935±0.0151*	116.7488±0.0088*	0.7855±0.0001*	0.0764±0.0001*

Mean±SD, * p < 0.05

was decreased in both cases by 29.7 and 47.1%, respectively. Time taken for the concentration of chloroquine to decrease by half ($t_{1/2}$) was decreased by 33.50 and 76.31% by the extract when administered 1 hour before and simultaneous with chloroquine, respectively. This shows that simultaneous administration of extract with chloroquine reduced $t_{1/2}$ twice as much as in when extract was administered one hour before chloroquine. This is not unexpected from the increase in elimination rate of 50.4 and 322.1%, respectively. Elimination rate in the simultaneous administration of both extract and chloroquine was far higher than in the administration of chloroquine one hour after the extract by a factor of 2.8. It is possible that the alkalination effect of the extract on the urine when extract was administered 1 h before chloroquine might have reduced compared to when extract and chloroquine were administered simultaneously.

The observed increase in the maximum concentration of chloroquine could be as a result of the increase in the rate of absorption in both cases. More rapid absorption is known to increase the peak plasma concentration. Simultaneous administration of extract and chloroquine raised the percent increase in C_{max} (18.5%) twice as much as that of administration of extract one hour before chloroquine (8.65%). This may also be a consequence of the better absorption rate in the former over the latter case.

Apparent volume of distribution indicates the size of the pool of body fluids that is required if the drug were distributed equally throughout the body. V_d is characteristic of a drug. But certain pathologic or disease states may affect V_d . The extract in both cases of administration reduced V_d . The reduction is highest when extract and chloroquine were administered simultaneously. It is known that if binding to plasma proteins is marked, most of the drug will be maintained within the intravascular compartment and V_d will be small. There is no evidence from this work to attribute the reduction in V_d by the extract to this factor. However, it is possible that there might have been a binding interaction between components of the extract and chloroquine. And it is not surprising that the binding effect was higher when the extract and chloroquine were administered simultaneously.

Bioavailability is the rate and extent to which an active drug is absorbed and becomes available at the site of drug action. The plant extract significantly reduced the bioavailability of chloroquine when administered 1 h after (26.35%) and simultaneously with (66.78%) the extract. Reduction of bioavailability in the simultaneous administration of both extract and chloroquine was higher. This may be because of the significantly high increase in the rate of elimination (0.2330) than in the other case (0.0830).

These results show that the administration of the ethanolic leaf extract of *Telfairia occidentalis* affected the pharmacokinetics of chloroquine both when administered 1 h before or simultaneously with chloroquine. In almost all the parameters, the simultaneous administration of the extract with

chloroquine had more significant effect than when the extract was administered 1 h before chloroquine. This suggests that taking chloroquine immediately after a meal prepared with *T. occidentalis* may affect the pharmacokinetics and hence effectiveness of chloroquine. Therefore, a malaria patient on chloroquine therapy should be advised not to take chloroquine with or immediately after a meal prepared with *T. occidentalis*.

This is the first time the effect of *T. occidentalis* on pharmacokinetics of a drug is being reported. The results of this research further gives credence to the findings of other researchers on the effects of certain plants on the pharmacokinetics of some drugs as mentioned in the introduction.

It is also hereby suggested that the effect of other commonly eaten vegetables on the pharmacokinetics of chloroquine should be investigated. This may help us understand one of the factors responsible for the ineffectiveness of chloroquine and perhaps resistance to chloroquine.

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