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Bioavailability of sulphate and dihydrochloride salts of quinine

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Summary

A comparative bioavailability of three formulations of quinine was performed in 6 healthy male adult Africans after intravenous infusion of 600mg quinine hydrochloride in 0.9% saline over 4 hours and after single oral doses of 600mg quinine sulphate capsule, 600mg quinine dihydrochloride plain tablet and 600mg quinine sulphate sugar coated tablet. The drugs were given according to a randomised cross-over design. The quinine sulphate coated tablet was found to contain no quinine. There was no statistical significant difference ($P > 0.05$) in the plasma C_{max}, t_{max}, AUC and K_a values between the quinine sulphate capsule and quinine dihydrochloride plain tablet, although a considerable degree of inter- and intra-individual variability in the pharmacokinetic parameters was observed. The absolute bioavailability was 64.5 and 64.3% for the quinine sulphate capsule and the quinine dihydrochloride plain tablet respectively. The non-detection of quinine in the sugar coated tablet (obtained from Nigeria) confirms the presence of fake circulating antimalarial drugs in the country.

Résumé

Le comparatif biodisponibilité de trois formulations de quinine a été expérimenté sur 6 africans tous des hommes en bonne santé après une infusion intraveineuse de 600 mg de quinine hydrochloride salin pendant plus de 4 heures et apres une simple dose orale de 600mg de capsule de quinine dihydrochloride et 600mg de comprimé de quinine recouvert de sucre de sulfate. Les médicaments étaient donnés sur un plan au hazard. Le comprimé de quinine recovert de sulfate a été trouvè ne contenant aucune quinine. Il n'yavait aucune différence significant de statistique — ($P > 0.05$) dans le plasma Cmax, Tmax AUC et la valeur xa entre la quinine de capsule de sulfate et le comprime blanc de quinine dihydrochloride bien qu'un dégré considerable de variété d'inter et intra-individuel dans les parametres pharmacokinetique était observe. Le complet biodisponibilité etait de 64.5 et 64.3% pour le capsule de sulfate de quinine et le comprime blanc de dihydrochloride respectivement. Le manque de détection de quinine dans le comprimé charge de sucre (obtenu au Nigéria) confirme la présence de faux medicaments contre le paludisme en circulation dans le pays.

Introduction

In the face of growing chloroquine resistance, quinine has become increasingly employed in the treatment of multi-drug resistant falciparum malaria and is once-again recognised as first-line antimalarial agent in some parts of the world. In uncomplicated and in severe complicated malaria, quinine is usually administered orally and parenterally respectively. The oral formulations, usually as capsules or tablets of quinine sulphate, bisulphate, hydrochloride and dihydrochloride have bitter taste. In order to mark the bitter taste of the salts, sugar coated tablets have been developed. It has been claimed that sugar coating reduces bioavailability because the tablets may fail to dissolve[1,2,3]. Accordingly, it has been advised[3] that sugar coated tablets should be avoided.

A recent report of comparative bioavailability of three formulations of quinine showed no significant differences in the extent of absorption[4]. However, there is no published study of the bioavailability of quinine in Africans despite increasing use of the drug in the continent. Based on the low therapeutic index of this drug[5], its increasing generic availability and lack of published bioequivalency data in the African, the objective of this study was to compare the relative bioavailability of three commonly available

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formulations of quinine in this group. In addition, the absolute bioavailability of these formulations was compared with a commonly used intravenous formulation.

Methods

Subjects: Six healthy adult male volunteers between the ages of 13 and 22 and weighing between 55-60kg were studied, after giving written informed consent. The subjects underwent physical examination, electrocardiogram, blood and urine analysis, and were instructed to abstain from other medication 4 weeks prior to and during the period of the study. The study was approved by the Joint University of Ibadan, University College Hospital, Ibadan Ethical Committee.

Drugs: Quinine sulphate capsule (Eli-Lily and Co., Indianapolis, U.S.A.) control No. LAB50A was obtained courtesy of Dr. C.C. Campbell, CDC, Atlanta, Ga, U.S.A. Quinine dihydrochloride tablets (Plain) (Laboratoire Labaz, Ambares, France LOT82) was obtained from France, courtesy of Dr. P. Druilhe, Laboratories, Labaz, France. Quinine sulphate tablets (sugar coated) (Labelled Jannsen Pharmaceuticals, Belgium) was obtained from a local pharmacy shop in Calabar, Southeastern, Nigeria. Quinine dihydrochloride injection (Avion-Pharma, Hamburg, Germany) batch No. 4450 was obtained from Western Germany.

Drug schedule: Each of the subjects received the 4 formulations in turn according to a randomised cross-over design. Drug administration was carried out at fortnightly interval. Quinine injection was given as 600mg of the dihydrochloride in 500ml normal saline infused at a constant rate over 4 hours. The oral drugs were given as follows: 600mg of the sulphate capsule, 600mg of dihydrochloride plain tablets and 600mg of the sulphate sugar coated tablet. Each of these formulations contains approximately 500mg of quinine base per tablet or capsule.

The subjects fasted overnight beginning at midnight until 4 hours after the drug administration. The drugs were administered with 250ml water. Food and water were allowed freely 4 hours after drug administration.

Blood sampling: Venous blood (5ml) was obtained from a fore-arm vein immediately before and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 4.5, 5, 6, 7, 8, 9, 10, 24, 36, 48 and 72 h after commencing intravenous infusion. During oral study, blood. was obtained before and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48 and 72 h after drug administration.

Before and at hourly interval, the pulse rate, blood pressure and respiratory rate were measured. Electrocardiogram was done before and at 1 and 3 h after drug administration. The subjects were questioned and, where necessary, examined for the presence of adverse drug reactions.

Quinine assay: Quinine was assayed in plasma by a sensitivity and specific high performance liquid chromatography (HPLC) method. Plasma (1ml) and the internal standard primaquine (aqueous solution, 100 µl of 100 µg/ml) were alkalinised with 5M sodium hydroxide solution. Perchloric acid (0.3ml) was added. The mixture was then extracted with 5ml of diethylether and the mixture vortexed for 60 seconds. The organic layer was separated following centrifugation at 2,000 revolutions per minute for 10 minutes. Hydrochloric acid (100 µl of 0.1N) was added to 2ml of the organic layer and the mixture vortexed for 50-60 seconds and centifuged at 2,000 revolutions, per minute for 10 minutes. The upper ether layer was removed and 20 µl of the quinine extract injected into the HPLC with fluorescence detection.

The mobile phase comprised 0.2M potassium diphosphate, acetonitrile and methanol in the ratio of 80:10:10 (v/v). To 100ml of this mixture was added 0.8ml perchloric acid giving a pH of 2.8. The column was u Bondapak C_{18}, 3.9 x 300mm. The fluorescence detector was set at 254nM. The compounds eluted from the column in the following order: quinine metabolite, quinine and primaquine. The flow rate was 1.2ml min^{-1}. The retention times for quinine and internal standard were 10 and 12 minutes respectively. The lower limit of detection was 20µg/ml. Recoveries over the concentration range of 1µg/ml to 10µg/ml were 92-102%. Coefficients of variation within sample were 5.5 and 3.5% and between samples 4.5 and 1.5% for concentrations of 10ng and 10µg/ml respectively. Calibration plots were linear ($r = 0.9994$) up to 5µg/ml.

Data analysis: The concentration-time data were analysed using a two-compartment open model and a computer programme MK Model[6]. The time to reach peack plasma concentration (t_{max}) and the peak plasma concentration achieved (c_{max}) were obtained from the plasma drug concentration-time curves by computer intrapolation. The terminal half-life ($t_{1/2}$) in plasma was calculated by linear regression of the log concentration-time plots using the last four or five

points. The area under the plasma concentration time curve (AUC) was estimated by using trapezoidal rule. The area to infinite time was added by integration of (C_{tn}/β), C_{tn} is the last value of quinine concentration on the calculated β slope, and β is the slope of the least squares regression line of the log concentration-time plot. The absorption rate constant was calculated by the method of residuals.

Values are given in the test and Tables as means ± sd. Differences between means were tested for significance using student's t test and P values less than 0.05 wre taken as significant.

Results

The change in plasma concentration with time after administration of the different formulations is shown in Fig. 1. The individual C_{max}, t_{max}, K_a and AUC are shown in Table 1. The absolute bioavailability of the different formulations was 64.5, 64.3 and 0% for the quinine sulphate capsule, quinine dihydrochloride plain tablet and quinine sulphate sugar coated tablet respectively. The 'non-bioavailability' of the last formulation was due to the fact that no quinine was present in the preparation. There were no significant differences ($P > 0.05$) in AUC, C_{max}, t_{max}, and K_a between the quinine sulphate capsule and quinine dihydrochloride plain tablet, although there was a wide inter- and intra-individual variation in these values (Table 1). Only one subject reported headache of 30 minutes duration at the third hour of intravenous infusion. Plasma quinine concentration during this period was 4.5μg ml^{-1}. Other subjects who attained similar concentrations did not report any subjective symptom. Otherwise, all the formulations were well tolerated. Blood pressure and pulse as well as electrocardiogram monitored throughout the study remained within normal limits.

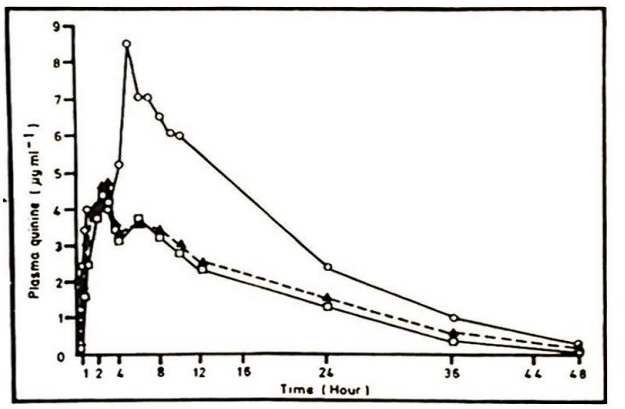

Fig. 1: Mean plasma quinine concentrations after infusion of 600mg quinine hydrochloride in 500ml normal saline over 4 hour (o——o) and after oral administration of 600mg quinine sulphate capsule (▲——▲) and 600mg quinine dihydrochloride plain tablet (■ ——■). The quinine sulphate sugar coated tablet (not shown here) contained no quinine.

Table 1: Plasma pharmacokinetic parameters in 6 healthy adult males following intravenous infusion of 500mg base quinine in 500ml normal saline over 4 hours and oral administration of 500mg base of 3 different formulations* of quinine (i.v. = intravenous infusin, QSC = quinine sulphate capsule, QDP = quinine dihydrochloride plain tablet)**

	C_{max} (ug ml^{-1})			T_{max} (h)			K_a h^{-1}			AUC (ug ml^{-1} h)			t1/2 (h)		
Subject	I.V.	QSC	QDP	I.V.	QSC	QDP	I.V.	QSC	QDP	I.V.	QSC	QDP	I.V.	QSC	QDP
1	5.54	6.30	2.80	10	2.5	4.0	—	2.54	1.84	89.61	114.74	70.82	19.9	15.62	12.47
2	16.29	5.85	2.20	7	2.0	4.0	—	2.35	1.92	239.44	88.74	48.32	10.82	10.87	6.54
3	10.13	4.93	1.44	5	2.0	1.0	—	2.26	1.91	121.23	81.16	62.66	6.85	8.95	11.35
4	9.44	4.51	8.9	5	2.5	4.0	—	2.47	2.52	157.02	61.23	134.55	10.00	7.87	16.20
5	8.57	5.79	2.83	7	3.0	1.0	—	2.31	2.10	132.87	66.88	70.42	13.10	7.86	12.05
6	7.91	12.67	12.40	6	4.0	2.0	—	3.84	3.21	126.12	145.94	170.31	11.05	9.34	9.69
Mean	9.64	6.67	5.06	6.66	2.66	2.66	—	2.62	2.25	144.38	93.11	92.84	11.95	10.05	11.38
s.d.	3.61	0.75	4.49	1.86	0.75	1.50	—	0.60	0.53	51.37	32.01	48.21	4.39	2.93	3.19

* Quinine sulphate coated tablet obtained from Nigeria contained no quinine

** No significant difference ($P > 0.05$) in these parameters between QSC and DPH

Discussion

Because of its increasing use worldwide and low therapeutic index[5], emphasis has recently been placed on the importance of establishing biological equivalence of quinine formulations[4]. Since the bioavailability of quinine formulations depend on the rate and extent of absorption, we determined these factors in the present study by the analysis of pharmacokinetic parameters derived from plasma concentration-time profiles for quinine using different formulation. The results showed that although there was wide intra- and inter-individual variability in the pharmacokinetic parameters, both the quinine sulphate capsule and the quinine dihydrochloride plain tablets are bioequivalent as evidence by comparable mean AUCs, peak plasma concentrations (C_{max}), t_{max} and absorption rate constant. Although disintegration times for both the capsule and plain tablet formulations were not determined in this study, comparable mean plasma level of 1.8 and 1.5 at 0 h and 3.1 and 2.5 $\mu g\ ml^{-1}$ at 1h respectively for the capsule and plain tablet formulations suggest similar disintegration times, since plasma levels at these two times have been correlated with similar disintegration times for formulations of quinine and quinidine[1,7].

One of the problems of developing countries of Africa south of the Sahara is lack of adequate drug quality control systems. With increasing resistance of P. falciparum to chloroquine, steadily increasing generics of available alternative antimalarial drugs and poor drug monitoring systems, additional public health problems have been created for these countries. Thus, the sugar coated quinine tablet obtained from Nigeria contained no quinine. This phenomenon which we have labelled the 'fake drug syndrome' is a common public health problem in Nigeria, where, according to an estimate, as much as 60% of circulating drugs are fake, adulterated or expired drugs[8].

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References

1. Garnham JC, Raymond K, Shotton E, Turner P. The bioavailability of quinine. J. Trop. Med. Hyg. 1976; 79: 264-269.
2. Bruce-Chwatt LJ, Black RH, Canfield CJ, Clyde DF, Peters W, Wernsdorfer WH. Chemotherapy of malaria, 2nd edn. World Health Organisation Monograph Series, 1981 No. 27.
3. Bruce-Chwatt LJ, Black RH, Canfield CJ, Clyde DF, Peters W, Wernsdorfer WH. Chemotherapy of malaria, Revised 2nd edn. World Health Organisation Monograph Series, 1986 No. 27.
4. Jamaludin A, Mohammed M, Navaratnam V, Selliah S, Tan SC, Werndorfer WH, Yuen KH. Relative bioavailability of the hydrochloride, sulphate and ethyl carbonate salts of quinine. Br. J. Clin. Pharmacol. 1988; 25: 261-263.
5. White NJ. Drug treatment of falciparium malaria. Eur. J. Clin. Pharmacol. 1988; 34: 1-14.
6. Holford N. MK Model: An extended least square modelling program. 1986: Biosoft, Cambridge, U.K.
7. Strum JD, Collaizi JL, Jaffe JM, Martineau PC, Poust RI. Comparative bioavailability of four commercial quinidine sulphate tablets. J. Pharmaceut. Sci. 1977; 66; 539-541.
8. Annonymous. Nigeria: Anarchy in the drug market. Lancet, 1988; 1: 108.

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