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The effect of chloroquine on paracetamol disposition and kinetics

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The effect of chloroquine on paracetamol kinetics and disposition was investigated in six healthy male Ghanaian volunteers. Chloroquine administration shortened the time taken to reach peak plasma paracetamol concentration (t_{max}) in five of the volunteers. Peak plasma paracetamol concentration (C_{max}) was significantly increased by chloroquine administration. The area under the plasma paracetamol concentration–time curve was also significantly increased by chloroquine administration. There was, however, no effect of chloroquine on paracetamol metabolism.

Keywords chloroquine paracetamol pharmacokinetics

Introduction

Chloroquine is the most widely used drug for the prophylaxis and chemotherapy of malaria. It can cause gastrointestinal upsets and may thus influence gastric emptying and intestinal transit. Chloroquine appears to increase the gastric emptying time in rats (Varga, 1966), but it is not known whether it has similar effects in man. Patients with malaria are often given analgesics for the relief of joint pain, headache and fever, and their effects could be unpredictable if chloroquine alters gastric emptying and hence oral drug absorption. The present study was therefore undertaken to investigate the effects of a single dose of chloroquine on the disposition and kinetics of paracetamol in man.

Methods

Six healthy Ghanaian male volunteers participated in the study. Their mean age and body weights were 32.5 ± 13.0 years and 58.8 ± 4.9 kg, respectively. They took no medication, tobacco or alcohol for 2 weeks prior to or during the study. Informed consent of each volunteer was obtained and approval was given by the National Ethics Committee of Ghana before commencement of the study.

After an overnight fast, the bladder was emptied and each subject was given 1.5 g of paracetamol B.P. (Seward) dissolved in 100 ml of orange flavoured water. The subjects rested supine for 1 h before and for 4 h after drug administration. Coffee was allowed at 2 h and a light lunch was taken 4 h after ingestion of the paracetamol. Venous blood was sampled at 0, 5, 10, 15, 20, 30, 45, 60, 75 and 90 min and at 2, 3, 4, 5, 6 and 8 h after dosing with paracetamol. Timed urine collections were made for 24 h. Plasma and urine samples (20 ml) were stored at −20°C until analysed for paracetamol and its metabolites by high performance liquid chromatography (Adriaenssens & Prescott, 1978).

Two weeks later the study was repeated after intramuscular injection of 250 mg chloroquine phosphate (150 mg chloroquine base, GIHOC Pharmaceuticals, Accra) 1 h before dosing with paracetamol. Thus each subject acted as his own control.

Pharmacokinetic variables were calculated using standard methods (Gibaldi & Perrier, 1975). The area under the plasma concentration

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time curve (AUC) was estimated by the trapezodial rule (0–8 h) and the additional area to infinite time was determined from the relationship C_8/β. Results are given as means ± s.d. and comparisons were made using the paired Student's *t*-test.

Results

Following administration of paracetamol, peak plasma concentrations (C_{max}) ranged from 20.4–40.0 μg ml^{-1}). After pretreatment with chloroquine, peak concentrations were significantly greater, ranging from 34.9–52.7 μg ml^{-1} (mean 40.1 μg ml^{-1}) ($P < 0.002$, Table 1). The time to reach peak concentrations (t_{max}) ranged from 0.33–1.5 h (mean 0.78 h) with paracetamol alone and from 0.25 to 0.5 h (mean 0.39 h) after pretreatment with chloroquine. This difference was not statistically significant. The effects of chloroquine on the mean plasma concentrations of paracetamol during the first 2 h are shown in Figure 1. After chloroquine, the mean AUC increased from 109–133 μg ml^{-1} h ($P < 0.02$). Pretreatment with chloroquine had no significant effect on the plasma half-life (Table 1).

Chloroquine had no effect on the 24 h urinary recovery of paracetamol or on the proportion of the dose excreted as the sulphate, glucuronide, cysteine or mercapturic acid conjugates.

After paracetamol administration the 24 h mean urinary recovery of the drug and its metabolites in the volunteers was 61.4 ± 9.0% and the corresponding value when paracetamol was given after chloroquine pretreatment was 68.1 ± 6.3%. The mean percentage recoveries of paracetamol and its sulphate, glucuronide, cysteine and mercapturate conjugates were 3.6 ± 1.00%, 20.3 ± 3.9%, 33.1 ± 7.2%, 1.72 ± 0.80% and 2.65 ± 1.18% when the drug was administered alone and 3.45 ± 0.73%, 21.6 ± 4.9%, 37.3 ± 8.0%, 1.79 ± 1.2% and 2.59 ± 1.08%. respectively after chloroquine.

Discussion

Under the conditions of this study, chloroquine appeared to increase the rate of paracetamol absorption as judged by an increase in C_{max} and a decrease in t_{max}. However, it was not possible to calculate the comparative absorption rate constants since, after chloroquine treatment, there were only two data points before t_{max} was reached in four of the six subjects. Gastric emptying is an important rate-limiting step in the absorption of paracetamol (Clements *et al.*, 1978) and it was probably accelerated by the chloroquine. There appear to be species differences in this respect since an opposite effect was observed in the rat (Varga, 1966).

Chloroquine increased the area under the plasma concentration–time curve. The reason for this is not clear. A possible decrease in metabolic clearance of paracetamol or an increase in its apparent volume of distribution are equally plausible explanations. Chloroquine did not influence the extent of absorption of paracetamol as shown by the overall recovery of the drug and its metabolites. The pattern of urinary excretion of paracetamol metabolites also was not influenced by chloroquine affording no evidence of selection inhibition of metabolism.

The magnitude of the effects produced by a single dose of chloroquine on paracetamol absorption and kinetics are unlikely to be of clinical significance. However, the possible effects of

Table 1 Peak plasma paracetamol concentration (C_{max}), time of peak concentration (t_{max}), half-life ($t_{1/2}$), and area under the plasma paracetamol time curve (AUC) following a single oral dose of paracetamol 1.5 g with and without pretreatment with chloroquine phosphate (CQ) 250 mg i.m

	C_{max} (μg ml^{-1})		t_{max} (h)		$t_{1/2}$ (h)		AUC (μg ml^{-1} h)	
Subject	−CQ	+CQ	−CQ	+CQ	−CQ	+CQ	−CQ	+CQ
D.K.O.	39.96	52.72	0.33	0.25	3.15	2.68	116.8	113.6
M.C.	29.32	36.31	0.50	0.33	2.91	4.82	92.6	127.7
J.A.B.	22.22	35.25	0.50	0.25	2.57	2.30	78.6	118.7
A.K.O.	20.42	42.14	1.50	0.50	3.78	3.52	108.9	125.8
F.Y.A.	30.77	39.47	0.33	0.50	3.27	3.70	126.3	155.8
F.D.G.	20.38	34.87	1.50	0.50	3.31	4.70	132.4	156.4
Mean	27.2	40.1	0.78	0.39	3.17	3.62	109.3	133.0
± s.d.	7.0	6.2	0.52	0.12	0.37	0.94	18.7	17.0

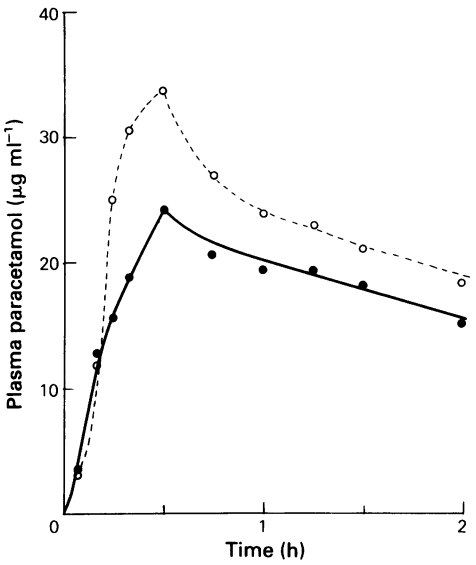

Figure 1 Mean plasma paracetamol concentrations (μg ml^{-1}) in six subjects following a single dose of 1.5 g with (o- - -o) and without (•—•) pretreatment with chloroquine phosphate 250 mg i.m.

multiple dosing with chloroquine (as used in the treatment of malaria) on drug disposition in man merit further study.

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