Earlier studies of quinine concentrations after intramuscular injection were encouraging,[11 25 28] although none of this work excluded the possibility of transient but toxic peak concentrations. Our results show that a loading dose results in therapeutic plasma concentrations within four hours of injection and that absorption is reliable in patients with moderately severe malaria without the risk of high peaks seen after intramuscular chloroquine (see accompanying paper, p 11). Further work is needed to assess the use of this route in severe, complicated malaria and in children. It is certainly not the ideal route for administration of quinine, but in the absence of the equipment or skills for intravenous infusion intramuscular quinine could be life saving; the risks have been exaggerated.

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Divided dose intramuscular regimen and single dose subcutaneous regimen for chloroquine: plasma concentrations and toxicity in patients with malaria

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Abstract

Adults with malaria in Sri Lanka were treated with parenteral chloroquine diphosphate, either 2·5 mg base/kg intramuscularly at 0, 1, 12, 13, 24, and 25 hours or 5 mg base/kg subcutaneously at 0, 12, and 24 hours. Both regimens were completed with oral chloroquine phosphate, 5 mg base/kg, at 36 and 48 hours. Mean peak chloroquine concentrations in the first 12 hours, which were 0·5 (range 0·3-0·6) mg/l (1·4 (0·9-1·7) mmol/l) with the intramuscular regimen and 0·3 (0·2-0·4) mg/l (1·0 (0·7-1·3) mmol/l) with the subcutaneous regimen (p<0·05), were reached in median times of 90 (65-90) minutes and 30 (30-60) minutes respectively (p<0·05) after the start of treatment. The mean area under the plasma concentration curve for the first 12 hours was 1·4 (0·9-2·1) mg/l.h (4·5 (2·8-6·4) mmol/l.h) after intramuscular administration and 1·8 (0·8-2·3) mg/l.h (5·7 (2·7-7·2) mmol/l.h) after subcutaneous administration (p>0·1). Mean maximum plasma concentrations were higher after intramuscular administration (0·6 (0·4-0·8) mg/l (1·7 (1·3-2·5) mmol/l)) than after subcutaneous administration (0·4 (0·4-0·5) mg/l (1·3 (1·3-1·5) mmol/l)) (p<0·05), but both regimens produced satisfactory plasma profiles. Chloroquine resistance was found in the only case of Plasmodium falciparum malaria.

Chloroquine is absorbed rapidly after divided dose intramuscular injection and single dose subcutaneous injection and does not cause hypotension or neurotoxicity in adults. Similar regimens should be evaluated in children before the parenteral use of this drug is abandoned.

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Introduction

A World Health Organisation (WHO) scientific group has recommended that the use of parenteral chloroquine should be abandoned world wide.[1] This arose from fears that patients with malaria who attended clinics after taking chloroquine at home would be at risk of serious toxicity if they were then given a chloroquine injection. Cases of sudden death after intramuscular administration of chloroquine were cited in support of this decision.[2-4] Abandoning the use of such a widely used and lifesaving drug is a serious matter. The WHO group was influenced by the knowledge that chloroquine was often given by unsupervised paramedical staff who failed to adjust the dosage to the patient's weight, but problems of pretreatment and poor use of injectable drugs apply to all antimalarial drugs, not just chloroquine.[5] Preliminary data suggested that chloroquine given intramuscularly was no less effective and no more toxic than quinine given parenterally.[6 7] Chloroquine has been well tried and excellently tolerated in pregnancy and unlike quinine does not cause hypoglycaemia.[8 9] A serious problem has been the complete lack of information about the pharmacokinetics and toxicity of the drug after parenteral administration.

It is now clear from studies on volunteers that cardiovascular toxicity is likely to occur only when chloroquine enters the circulation very quickly—for example, after intravenous injection.[10 11] Rapid absorption after intramuscular injection, a phenomenon observed in animals,[12] is suspected to have been responsible for the collapse and death of African children who were prone to hypotension because of dehydration and generalised vasodilatation.[2-4] This type of collapse, however, though often discussed, is virtually undocumented.[13]

We report here the plasma concentrations achieved with, and the toxicity of, parenteral regimens in adults with malaria—namely, divided dose intramuscular injections and single dose subcutaneous injections.

Patients and methods

At Anuradhapura General Hospital, Sri Lanka, patients were recruited for study if they had malaria that required parenteral treatment. Patients were excluded if they were younger than 15 or older than 65; had a history of recent antimalarial treatment; had a mixed infection; were pregnant; or had a second disease. All patients gave informed consent to investigation and treatment. The study was approved by the Ministry of Health and by the hospital medical staff. Patients were admitted to hospital and weighed, and a full history and results of examination were recorded on standard forms. Parasites were counted in thick films. Blood pressure and pulse were recorded before the start of treatment, every 15 minutes for one hour, and then every 30 minutes.

Chloroquine diphosphate (May and Baker) was given in a total dose of 25 mg base/kg body weight to patients by one of two regimens chosen randomly. In the divided dose intramuscular regimen chloroquine 2·5 mg base/kg was injected into the quadriceps muscle (anterior thigh of alternate legs) on admission and then one, 12, 13, 24, and 25 hours later. In the single dose subcutaneous regimen chloroquine 5 mg base/kg was injected sub-

cutaneously at the lateral aspect of the thigh of alternate legs on admission and then 12 and 24 hours later. In both groups of patients the course was completed by giving oral chloroquine phosphate 5 mg base/kg at 36 and 48 hours. At 15 minute intervals for one hour after the first dose, and then every 30 minutes, patients were asked about pain at the site of injection and other side effects. Injection sites were examined before every injection and then daily until the patients were discharged.

Blood samples were taken, through an indwelling intravenous Teflon catheter kept patent with heparinised saline, before treatment; at five, 15, 30, 60, and 90 minutes and two, three, and six hours after the first dose; before and one and two hours after the doses at 12 and 24 hours; and before the last dose at 48 hours. Additional samples were taken at 65 and 75 minutes in patients given intramuscular chloroquine. Blood, dispensed from plastic syringes into plastic heparinised tubes, was centrifuged at 360 g for 15 minutes. Plasma, free of the buffy coat, was transferred in plastic pipettes to plastic phials and stored at −20°C for one to two weeks before being transported on dry ice to Liverpool, where it was stored at −70°C until assayed by high performance liquid chromatography.[14] All glassware was treated with dichlorodimethylsilane (5% vol/vol in toluene) to minimise drug absorption.

Plasma chloroquine concentrations were analysed with a Hewlett-Packard HP-975 programmable calculator. Statistical comparisons were performed with the Mann-Whitney U test.

Results

Fourteen patients with *Plasmodium vivax* malaria and one patient with *P falciparum* malaria, all of whom had a history of fever and rigors, were studied. All but one were feverish (temperature >37·5°C) at the time of the first chloroquine injection. No patient had chloroquine detectable in pretreatment plasma analysed subsequently in Liverpool. The two groups receiving intramuscular and subcutaneous chloroquine were comparable (p>0·1) for age, ratio of men to women, weight, parasitaemia, and total dose of chloroquine given (table).

Intramuscular chloroquine—All patients complained of pain at the site of injection, but none thought it severe; it lasted from 15 minutes to two hours. They did not complain of discomfort on moving the muscle once the pain had subsided, and none had any sign of induration or abscess formation. There was a non-significant fall (p>0·05) in blood pressure 30 and 90 minutes after the first injection (table), and no patient had visual or other neurological symptoms or signs. Plasma chloroquine concentrations (fig 1) varied considerably among patients. Absorption was rapid, and in five of the
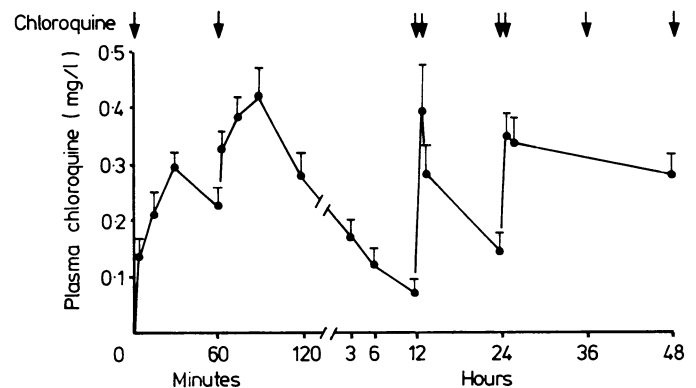

Chloroquine

FIG 1—Plasma chloroquine concentrations after intramuscular injection (2·5 mg base/kg body weight) at 0, 1, 12, 13, 24, and 25 hours and oral administration of chloroquine phosphate (5 mg base/kg) at 36 and 48 hours. Values are means (SEM).

Conversion: traditional units to SI—1 mg chloroquine≈3 mmol.

seven patients plasma concentrations at 30 minutes exceeded those at one hour. The mean peak plasma chloroquine concentration during the first 12 hours was 0·5 (range 0·3-0·6) mg/l (1·4 (0·9-1·7) mmol/l) and was reached a median of 90 (65-90) minutes after the first injection. The mean peak concentration after the second divided dose (given at 12 and 13 hours) was 0·5 (0·3-0·6) mg/l (1·4 (0·9-1·7) mmol/l). The mean highest concentration (0·6 (0·4-0·8) mg/l (1·7 (1·3-2·5) mmol/l)) was reached 30 minutes to 25 hours (median 90 minutes) after the start of treatment.

Subcutaneous chloroquine—Subcutaneous injection did not seem to be any more or less painful than intramuscular injection. There was no fall in blood pressure and no systemic effects. Figure 2 shows the plasma chloroquine

Details of patients and chloroquine administration. Figures are means (ranges) except where indicated

|	Intramuscular regimen (n=7)	Subcutaneous regimen (n=8)
Age (years)	23·9 (17-31)	27·1 (20-53)
Men:women	5:2	6:2
Weight (kg)	44·9 (35·5-49·0)	46·8 (41·0-56·0)
Parasitaemia (geometric mean/µl)	10 514 (4774-23 874)	5976 (4146-38 197)
No of febrile patients (temperature>37·5°C)	7	7
Temperature (°C)	38·4 (37·7-39·2)	37·8 (36·8-38·5)
Pulse (beats/min)	75 (56-84)	83 (60-120)
Mean (SD) blood pressure (mm Hg):		
Systolic (on admission)	103 (11)	102 (14)
Diastolic (on admission)	70 (12)	69 (10)
Systolic (at 30 minutes)	99 (7)	104 (14)
Systolic (at 90 minutes)	97 (12)	103 (12)
Chloroquine dose (mg base):		
First 24 hours	448 (354-490)	467 (410-524)
Total	1122 (888-1275)	1164 (1022-1400)
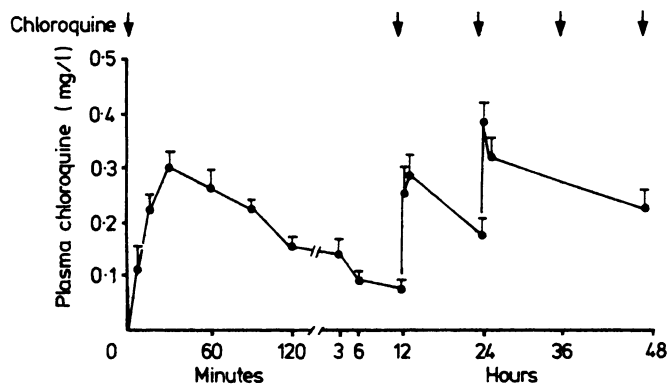
FIG 2—Plasma chloroquine concentrations after subcutaneous injection (5 mg base/kg) at 0, 12, and 24 hours and oral administration of chloroquine phosphate at 36 and 48 hours. Values are means (SEM).

Conversion: traditional units to SI—1 mg chloroquine≈3 mmol.

concentrations. Absorption was rapid. The mean peak plasma concentration during the first 12 hours was 0·3 (0·2-0·4) mg/l (1·0 (0·7-1·3) mmol/l) and was reached a median of 30 (30-60) minutes after injection. The highest concentrations, which averaged 0·4 (0·4-0·5) mg/l (1·3 (1·3-1·5) mmol/l), were found 13 hours (in two patients), 14 hours (two), and 25 hours (four) after the first injection.

Comparison of regimens—Plasma chloroquine concentrations were not significantly different between the two regimens at five, 15, 30, and 60 minutes. The time taken to reach maximum concentration in the 12 hours after the start of treatment was significantly shorter for the subcutaneous regimen (p<0·05), but the overall peak concentration was significantly higher after the intramuscular regimen (p<0·05). There was no significant difference between the two regimens in the areas under the plasma concentration curves for the first 12 hours (subcutaneous: mean 1·8 (0·8-2·3) mg/l.h (5·7 (2·7-7·2) mmol/l.h); intramuscular: 1·4 (0·9-2·1) mg/l.h (4·5 (2·8-6·4) mmol/l.h) (p>0·1).

Therapeutic effect—All patients with vivax malaria responded well. The only patient with falciparum malaria, a 31 year old woman admitted with parasitaemia of 13 193 trophozoites/μl, responded to treatment by showing clearance of parasites at three days but returned on day 14 with recurrent parasitaemia.

Discussion

For decades intramuscular injection of chloroquine has been used throughout the tropics to treat malaria. By this method rural health workers have been able to treat patients who were vomiting or comatose, and the practice was rarely questioned, despite some reports of sudden death in children. In retrospect, it is surprising that the chemotherapy of a life threatening infection should have relied on a drug whose pharmacokinetics were so poorly understood. Until recently there had been no attempt to define the pharmacokinetics and toxicity of chloroquine in man, yet there were sufficient data from animal experiments and patients who had taken overdoses to suggest that cardiovascular poisoning was a serious risk.[12 15] When the WHO became aware of a high incidence of self medication with chloroquine[16] it decided to recommend that parenteral use of this drug should be abandoned because it feared that toxic concentrations could result if intramuscular injections were given.[1] After this decision there was much uncertainty about parenteral chemotherapy for malaria; chloroquine has had a generally good record of safety for nearly 40 years and the only alternative drug, quinine, is also potentially toxic.

The critical data needed to make an informed decision about chloroquine were the kinetics of absorption and disposition. This deficiency has been partly corrected by recent studies in volunteers and patients with malaria. After intravenous injection transient but very high plasma chloroquine concentrations occur and all subjects report side effects such as dizziness and blurred vision.[10 11] Hypotension and prolongation of the electrocardiographic QRS interval were detected in one study, in which cardiovascular effects were specifically sought.[11] Absorption in animals after intramuscular injection was rapid,[12] and the present study shows that this is also true in man, whether the drug is injected into muscle or sub-

cutaneous tissue. Peak chloroquine concentrations were significantly higher and were reached sooner during the intramuscular regimen, but relative bioavailability as judged by the area under the plasma concentration curve was similar. Peak concentrations were lower than those detected in volunteers given intravenous injections of similar doses,[10] and the patients with malaria did not experience a change in blood pressure or neurotoxic effects.

Studies in areas where P falciparum remained fully sensitive to chloroquine have shown no advantage for quinine, which is more expensive.[6 7] Both drugs have potential cardiovascular toxicity,[15 17] particularly when given in overdose or by rapid intravenous injection.[18] Quinine has the additional risks of refractory hyperinsulinaemic hypoglycaemia,[19] especially in pregnancy,[8] an association with blackwater fever,[20] and the potential for damage to tissue, even when injections are sterile.[21] Chloroquine has an excellent safety record in pregnancy,[22] and cerebral malaria in children has responded well to parenteral chloroquine.[23] Chloroquine was rapidly absorbed after subcutaneous injection in these Sri Lankan adults and in Zambians (N J White et al, unpublished findings), but in severe malaria with shock cutaneous perfusion may be sufficiently poor to dangerously impede systemic absorption of the drug. Under circumstances where therapeutic blood concentrations must be reached as quickly and reliably as possible, such as in cerebral malaria, slow intravenous (or even continuous) infusion is the best way to give chloroquine parenterally.[24] As a compromise where intravenous equipment is not available divided dose intramuscular injections, correctly adjusted for weight, allow therapeutic chloroquine concentrations to be reached quickly and reduce the risk of transient but potentially dangerous peaks that could occur if 5 mg base/kg was injected as a single dose. In shocked patients, however, absorption of chloroquine from muscle may be inadequate so this route should not be relied on unless it is impossible to set up an intravenous infusion.

Studies of intravenous chloroquine injection have suggested that dangerous concentrations occur when the drug enters the circulation more rapidly than it can be dispersed.[11] This could happen if absorption after intramuscular injection was particularly rapid, and this possibility must be investigated in children. Recent treatment with chloroquine could increase the risk of high concentrations,[16] but the rate of entry of the drug into the circulation, rather than the dose, seems to be the most important determinant of acute toxicity.[11]

Debate over the relative merits of quinine and chloroquine will continue while P falciparum remains sensitive to chloroquine in some parts of the world. The rapid spread of chloroquine resistance westwards in Africa and Asia (shown by the patient with falciparum malaria described above and other recent reports[25]) may ultimately make this discussion redundant. For the time being, however, quinine is not an ideal substitute for chloroquine world wide. Radical cure with quinine alone is difficult to achieve, as the drug can cause serious toxicity, and it has never been shown to be superior to chloroquine for infections sensitive to chloroquine. Acute chloroquine toxicity seems to be predictable and can be circumvented by controlled administration. There are too few alternative drugs for us to abandon chloroquine for the treatment of severe malaria; the recommendation to do so should be revised.

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SHORT REPORTS

Ultrasound diagnosis of bile duct calculi

Diagnosing choledocholithiasis by ultrasound is difficult and most series have reported sensitivities of 8-30%.[1][2] The calibre of the common duct is not a reliable indicator since up to a third of patients with choledocholithiasis have ducts of normal size[3] and, conversely, dilated but non-obstructed ducts are common in patients who have had cholecystectomy.[4] We investigated the role of real time ultrasound as a screening test for selecting patients with suspected biliary tract disease for retrograde cholangiography and aimed at determining whether we could reliably predict or exclude bile duct disease by combining the ultrasonic findings in the bile duct with those in the gall bladder and the results of biochemical liver function tests.

Patients, methods, and results

A total of 104 patients (41 men, 63 women; mean age 60 years, range 21-88) had an ultrasound examination performed by one of two experienced radiologists

some abnormality or was technically unsatisfactory in 19 of 27 patients with dilatation of the common duct only or other biliary disorders besides choledocholithiasis its specificity was only 68%.

Gall bladder calculi on ultrasound and liver function abnormalities—In 47 patients with gall bladders in situ gall bladder calculi were significantly more common in those with choledocholithiasis than in those without (12/16 (75%) *v* 11/31 (35%); $\chi^2 = 6.67$; p<0.01), as were liver function abnormalities in those with choledocholithiasis compared with those with normal cholangiograms (31/36 (86%) *v* 7/39 (18%); $\chi^2 = 34.8$; p<0.001). The predictive values of normal ultrasonic appearances in the gall bladder and normal liver function values in excluding choledocholithiasis were 83% and 86% respectively.

Comment

Calculi are common in the bile duct, particularly in the elderly, when the presentation is often atypical and non-specific, and retrograde cholangiography is not always available for accurate diagnosis. Conversely, many cholangiograms to exclude stones in the common duct are performed unnecessarily as a result of the reported unreliability of ultrasound.

Results of common duct and gall bladder ultrasound and liver function tests

Findings on cholangiography	Results of common duct ultrasound (n=102)*		Results of gall bladder ultrasound (n=47)		Liver function values (n=75)	
	Normal	Abnormal or technical failure	Calculi present	Calculi absent	Normal	Abnormal
Calculi	1	35	12	4	5	31
No calculi	45†	21‡	11	20	32	7
Total	46	56	23	24	37	38

*Two patients with indeterminate duct calibre on cholangiography excluded from further analysis.

†Thirty seven patients had a normal cholangiogram.

‡Nineteen patients had other disease or dilatation of common duct only.

before retrograde cholangiography. Particular note was taken of the presence of calculi in the gall bladder and common duct and the calibre of intrahepatic and extrahepatic ducts. The upper limit of normal calibre of the common duct was 6 mm on ultrasound and 10·5 mm, corrected for magnification, on cholangiography. The ultrasound was deemed a technical failure when no part of the common duct was visualised, though in some of these cases the gall bladder was examined. All patients had biochemical liver function tests performed within 24 hours of the examinations. The table summarises the results.

Ultrasonic findings in common duct—Of 36 patients with calculi in the common duct detected by cholangiography, ultrasound correctly identified 20, in three of whom the duct was of normal calibre, giving a sensitivity of 56%. A further 10 had a dilated common duct diagnosed correctly, so that 83% of patients with calculi in the common duct had some abnormality of the duct noted at ultrasound. If five patients whose ultrasound examination was technically unsatisfactory are excluded this figure rises to 97%. Of 39 patients with normal cholangiograms, ultrasound was in agreement in 37, giving a predictive value of a normal finding in excluding choledocholithiasis of 98%. Nevertheless, because ultrasound showed

In this series we have shown how radiologists with a special interest can improve sensitivity enough to make ultrasound a valuable screening test for choledocholithiasis. In practical terms, if ultrasound visualisation of calculi in the common duct or dilatation or a technically unsatisfactory examination were taken as criteria for proceeding to direct cholangiography only a single patient with choledocholithiasis would have been missed and only 14 of 104 cholangiograms would have been "unnecessary." Of particular interest, however, was the combined predictive value of an ultrasonically acalculous gall bladder and normal liver function results in excluding choledocholithiasis—100% in this series—since all patients with choledocholithiasis who had an intact gall bladder had either cholelithiasis or abnormal liver function, or both.

In conclusion, this study shows that, though stones in the common duct remain elusive to ultrasound, real time ultrasonography, performed by experienced radiologists, and biochemical liver function tests provide a