Quinine Dosage and Serum Levels in Falciparum Malaria

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BACKGROUND: The World Health Organization has emphasized the need for studying the pharmacology of antimalarial drugs in patients with falciparum malaria (1). Quinine is the only rapidly acting drug for chloroquine–resistant falciparum malaria. In healthy volunteers, quinine by intravenous infusion produced higher plasma quinine levels than did oral quinine (2).

We compared the serum concentrations of quinine following a single dose of one of the three modes of administration, (intravenous infusion, intramuscular injection and tablets) in patients with falciparum malaria, since no information was available on this subject. Serum quinine levels were also determined following repeated administration of the drug at 8 or 12 hour intervals, to determine the optimum dosage interval.

DESCRIPTION: Patients at Trad Provincial Hospital with falciparum malaria comprised the study group. Trad is in a remote area of Thailand 400 km from Bangkok. Quantitative parasite counts on thick blood films were made at least once daily (3).

Serum quinine levels were determined in 73 people following a single dose of the drug; sera were collected before dosing and usually 1, 2, 4 and 8 hours after the oral or intramuscular dose or after the beginning of an infusion. Twelve and 24 hour specimens were collected in a few patients. Thirteen patients were excluded from analysis because quinine was detected in the serum on admission. Sera could not be collected after 10 PM, so complete 1–8 hour data were only available on 35 patients. For technical reasons, urine could not be collected. The patients were randomly assigned to one of five dose regimens: two intravenous (two or four hour infusion), two oral (coated or plain tablets) and one intramuscular. The patients in each group were comparable with respect to age (overall mean 23.7 years) and weight (overall mean 51.8 kg).

Intravenous infusions (IVQ) consisted of 490 mg base (2 ml) of quinine dihydrochloride (The Vitarine Company, New York) injected into an infusion bottle containing 500 ml normal saline. The bottles were infused over a two or four hour interval. All were calibrated and the rate of flow was checked frequently to maintain a constant infusion rate of 125 ml or 250 ml each hour.

The enteric coated tablets of quinine sulfate (Strong Cobb Arner, Cleveland) contained 270 mg quinine base. The usual dose was 540 mg. The plain uncoated tablets (Government Pharmaceutical Organization, Bangkok) contained 250 mg base. The usual dose was 500 mg.

Intramuscular quinine (IMQ) was administered as quinine dihydrochloride (same preparation as used for intravenous therapy) in a dose of 490 mg quinine base (2 ml). The injections were made deeply in the upper and outer quadrant of the buttock.

Serum quinine levels following multiple dosing of the drug were determined in 31 patients (18 of whom had been studied following the initial dose). Nineteen patients received quinine at full dosage every 8 hours and 10 patients every 12 hours. Two patients received half–dosage quinine every 8 hours. With very few exceptions, all doses following the initial dose were oral. In multiple dose studies sera were collected at the time of dosing and at other times (e.g. 1, 2, 4, 8 and 12 hours after a dose). Serum quinine concentrations were determined by the benzene extraction method (4). Measurements were performed using an Aminco–Bowman spectrophotofluorometer (350 mμ. activation; 450 mμ. fluorescence). The parenteral and oral formulations of quinine were assayed and found to contain the designated amount of quinine base ($\pm$ 2 percent).

The half—life (T/2) of quinine was determined by plotting the serum concentrations of quinine against time on semi—logarithmic paper. Data from the single—dose studies were compared using analysis of variance. Following the overall analysis of variance, individual F tests were conducted to determine the location of mean differences (5, 6).

Single Dose: Complete data (serum levels at 1, 2, 4 and 8 hours after the dose) were available on 35 patients. There were seven patients in each of the five treatment groups. The mean serum quinine concentrations for each group are shown in Table 1. The analysis of variance indicated significant differences between the modes of administration and between the hours of sampling (Tables 2 and 3). One hour after initiation of the dose, the two hour infusion produced a significantly greater serum quinine concentration than did intramuscular quinine ($p<0.01$) which produced a significantly greater level than plain tablets ($p<0.01$). Four hours after initiation of the dose the four hour infusion produced a greater serum level than coated tablets ($p<0.05$). At eight hours, coated tablets produced a higher level than the intramuscular injection ($p<0.05$). The serum quinine concentrations following intravenous or oral administration were not significantly different at eight hours (Figure 1).

Serum quinine levels were not available at 12 hours for all 35 patients: the data were pooled (Figure 1). It is noteworthy that the serum quinine concentration 12 hours after dosing was about 6 mg per L following either intravenous or oral therapy.

Details on each of the regimens are now given.

Two Hour Infusion: Initially 10 men received a two hour infusion. Quinine was detected by later testing in the admission serum of three of these men, two of whom developed severe cinchonism (quinine toxicity) at the end of the infusion. Seven men had no quinine in the serum on admission and the average results on these patients were used in the analysis (Table 1). One and two hours after the beginning of the infusion, greater serum quinine levels occurred than with any other regimen. Thereafter the results were similar to those obtained with the four hour infusion. In one patient the serum quinine peaked at 10.8 mg per L at two hours and decreased slowly to 5.7 mg per L at 22 hours. This data suggests a half—life (T/2) of 21 hours. The clinical response (e.g. fever, parasitemia) to the two hour infusion was excellent; however, cinchonism was more common than with any other regimen.

Four Hour Infusion: Greater serum quinine concentrations were achieved with the four hour infusion than with oral or intramuscular quinine. In most patients the clinical response was excellent.

One patient, who was jaundiced, became aphasic during the infusion and was struggling and comatose at the end, at which time the serum quinine level was 8.8 mg per L. Sixteen hours later he could speak and since no further therapy had been given, a second quinine infusion was begun. During the second infusion he again became aphasic. The patient then received a single dose of pyrimethamine with sulfadoxine (Fansidar) and made a steady recovery. Neurotoxic hypersensitivity to quinine was diagnosed. In the other patients, the four hour infusion caused minimal side—effects.

Coated Tablets: The mean serum concentration of quinine one hour after the dose was only 0.8 mg per L. A peak serum quinine level of 7.6 mg per L occurred at four hours.

The clinical response was unsatisfactory in one patient; four hours after dosing his serum quinine was 6.1 mg per L. He complained of weakness, dizziness, cough and abdominal pain. Three episodes of diarrhea had occurred since admission. The patient improved after 250 mg quinine was infused, although further serum quinine levels were not obtained. One patient developed urticaria on the face and chest four hours after dosing that persisted for several hours and was attributed to the quinine. Mild cinchonism occurred in several patients.

Plain Tablets: The mean serum quinine levels after plain tablets were higher than after coated tablets at one and two hours but lower at four and eight hours. With seven patients in each group the one hour

data were not significantly different (Table 1). One hour data was available on several other patients not included in the group of 35, because not all 2–8 hour specimens had been obtained. In a total of 12 patients who received coated tablets, the mean one hour level was 0.7 mg per L. In 12 patients who received plain tablets, the mean level was 2.7 mg per L. The difference is significant ($t = 2.5$, $p < 0.05$).

In one patient the clinical response was unsatisfactory. Coma supervened two hours after therapy when the serum quinine level was only 0.4 mg per L. Thereafter the absorption of quinine was much improved (serum quinine level at four hours was 10.6 mg per L). The plain tablets often caused mild cinchonism but no serious toxicity was encountered.

Intramuscular Injection (IMQ): The serum concentration–time curve following intramuscular quinine was flat and did not rise appreciably above 6 mg per L.

One patient had a poor clinical response. Following the injection at 1100 hours, his parasite count increased from 12,000 to 217,000 per cu.mm. at 1700 hours. His serum quinine concentration was then only 3.1 mg per L. Intravenous quinine was then infused with a satisfactory response.

Multiple Dose Studies: Eighty percent (16/19) of the patients who received quinine at eight hour intervals developed some degree of cinchonism and in most patients this was associated with serum quinine concentrations assumed to be in the toxic range (over 10 mg per L). Only 30 percent (3/10) of the patients on 12 hour dosing developed cinchonism. The difference is significant (Chi square $= 6.9$, $p < 0.01$).

An example of overdosage with quinine given every 8 hours is shown in Figure 2. Early in therapy a high fever was associated with a raised serum bilirubin and a very high concentration of serum quinine (17.1 mg per L). Improvement was associated with a decrease in fever and bilirubin.

An example of an optimum response to quinine given every 12 hours is depicted in Figure 3. Clinical improvement was associated with a decrease in serum bilirubin and in serum quinine despite constant therapy. The approximate half–life (T/2) decreased from 21 to 14 to 12 hours during therapy.

On the other hand, in two other patients, therapeutic concentrations of serum quinine were maintained with a half–dose (one tablet) given every 8 hours.

The average half–life of quinine in falciparum malaria, derived from all available data on 17 patients was 18.8 hours (range 12–31).

DISCUSSION: The serum concentrations of quinine following oral therapy were low in relation to those following intravenous therapy for the first four hours after dosing. Thereafter the serum levels were the same. These data confirm the clinical impression that the intravenous route is more effective than the oral route for at least the first dose of quinine in falciparum malaria. Plain tablets produced significantly greater serum concentrations than coated tablets one hour after dosing. If the first dose has to be oral then plain are preferable to coated tablets. There was no evidence that cinchonism was less common in the patients who received coated rather than plain tablets.

Intramuscular quinine produced a significantly higher one hour serum quinine concentration than did oral quinine, and might occasionally be preferable to oral quinine for the first dose in situations where intravenous infusions are not available. However we have seen several patients in whom IMQ was clearly less effective than IVQ. The average serum quinine level following IMQ barely rose above 6 mg per L in distinction to the other modes of administration. The conclusions are that, in this study, 6 to 10 mg per L was the usual therapeutic range for quinine and that IMQ did not always produce sufficiently high levels. The bioavailability of quinine was least by the intramuscular route, a situation analogous to that for digoxin (7) and diphenylhydantoin (8). One dose of IMQ may be satisfactory in mild cases of falciparum malaria but repeated dosing is not indicated because gluteal abscesses may be produced (9).

intravenous infusions, either of two or four hours duration, produced serum quinine concentrations above 6 mg per L from the first hour onwards. The two hour infusions naturally produced higher levels but also more frequently caused toxicity. A two hour infusion can be considered for the initial dose but not for maintenance therapy. In two patients with quinine in the serum on admission, the two hour infusion produced very high serum quinine levels with toxicity. We have given IVQ with infusion times from 1 to 16 hours (10, 11). Lengthy infusions can cause arm discomfort and be inconvenient for the patient. The four hour infusion is the optimum form for quinine administration since therapeutic but not toxic levels of serum quinine are usually produced.

In this study the average half-life (T/2) of quinine was 19 hours in falciparum malaria which compares with the T/2 of 10 hours in healthy volunteers that can be deduced from another study (2). The T/2 of quinine is greater in volunteers with falciparum malaria than in the same volunteers without malaria (12). Thus in falciparum malaria the metabolism of quinine may be impaired presumbly due to liver dysfunction since quinine is mainly metabolized in that organ (13). Conversely quinine (2) or, its optical isomer, quinidine (14), can cause liver damage. A vicious cycle may occur: if a patient with falciparum malaria has hepatitis, the half-life of quinine is prolonged; thus routine doses of quinine may result in toxic levels of serum quinine; the latter may result in greater damage to the liver; the metabolism of quinine is thus further impaired; consequently even greater levels of serum quinine result.

Therefore, in most patients with falciparum malaria, lower or less frequent doses of quinine should produce the same serum quinine as higher doses in healthy patients. Our data confirm this theory. In many patients, maintenance therapy with full doses of quinine every 8 hours produced toxicity and high serum quinine levels, whereas quinine every 12 hours produced a satisfactory clinical response and therapeutic levels. This is not surprising since the average serum quinine level was still about 6 mg per L 12 hours after the initial dose of oral or intravenous quinine. On the other hand, therapeutic concentrations of serum quinine can be maintained with a half-dose (one tablet) given every 8 hours. Dosing every 12 hours might produce greater fluctuations of serum quinine concentration than will dosing every 8 hours; however, it is not known whether fluctuation or constancy in the serum quinine level is more effective. In tropical practice, drugs are usually given three times a day (e.g. 0800, 1200 and 1700 hours) rather than every 8 hours, so administration every 12 hours is easier to accomplish.

In several patients, high serum quinine levels occurred early in therapy, but despite constant maintenance therapy, a sharp decrease occurred associated with improvement in clinical state, fever and hepatic function. Other studies have found similar results (15, 16). We attribute the decrease in serum quinine levels to improved metabolism of quinine consequent upon improvement in hepatic function.

Reduced doses of quinine (e.g. 600 mg base intravenously daily) must be administered in patients with falciparum malaria complicated by renal failure (17, 18). In those studies the impairment of quinine metabolism may have been partly due to concomitant hepatic damage.

Aphasia and coma were caused by quinine in one of our patients at a time when the serum quinine was only 8.4 mg per L. Coma in falciparum malaria is sometimes caused by quinine rather than by the disease (i.e. quinine coma). However "It is sometimes difficult to distinguish between true quinine toxicity and complications of the diseases for which the drug is given" (13).

The WHO recommends 650 mg (540 mg base) three times daily as the standard dose of quinine (i.e. six tablets daily) (1). However the labels on the bottles of tablets used in this study recommend three tablets daily for two days followed by two tablets daily for five days. The difference between six tablets and 2-3 tablets daily is considerable. The paradox can be explained by the fact that the WHO recommendation in based upon several studies with Americans in Vietnam whereas the manufacturer's recommendations probably take into consideration the lower average body weight of people indigenous to the malarious areas. U.S. soldiers weighing 75 kg usually tolerate about 1500 mg of quinine base per day (20 mg/kg) but the same dose in 50 kg Thais is 30 mg/kg.

Our studies indicate that 20 mg/kg/day is sufficient in the average patient with falciparum malaria. This is the dose recommended by Fletcher (9). One infusion of 10 mg/kg/day is probably the optimum dose for falciparum patients with severe renal, hepatic or cerebral complications. Thus the more seriously ill the patient, the lower should be the dose of quinine.

It is of interest that 15 percent of the patients (13/86) in the single dose study had detectable quinine in the serum on admission. This is an indication of the prevalence of therapy before admission. Quinine toxicity may be compounded if this possibility is not considered.

SUMMARY: Patients with chloroquine–resistant falciparum malaria were studied. In 35 patients serum quinine concentrations were determined 1, 2, 4 and 8 hours after the initial dose of quinine or after the beginning of an infusion. The patients were randomly assigned to one of five dose regimens: two hour intravenous infusion, four hour intravenous infusion, coated tablets, plain tablets and intramuscular injection.

Intravenous quinine was better absorbed than oral quinine from one to four hours but the serum levels were not significantly different at eight hours. A four hour infusion is the optimum method of administering the first dose of quinine. Intramuscular quinine produced a significantly greater serum quinine level than oral quinine at one hour but a significantly lower level at eight hours. Further patients were studied and it was shown that plain tablets produced a significantly greater mean serum quinine concentration than coated tablets one hour after dosing.

In Thai patients (average weight 50 kg), full dose quinine (540 mg base) every 8 hours often produced toxic serum concentrations, whereas dosing every 12 hours was optimal therapy but still produced cinchonism in 30% of patients.

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Table 1. Serum Quinine Concentrations (mg/L) Following Intravenous Infusion, Oral or Intramuscular Administration

Hour	Intravenous 490 mg/2 Hrs		Intravenous 490 mg/4 Hrs		Oral 540 mg/Coated		Oral 500 mg/Plain		Intramuscular 490 mg	
	No.	Mean ± SEM	No.	Mean ± SEM	No.	Mean ± SEM	No.	Mean ± SEM	No.	Mean ± SEM
0	7	0	7	0	7	0	7	0	7	0
1	7	8.7 ± 1.1	7	6.0 ± 0.6	7	0.8 ± 0.4	7	2.6 ± 0.9	7	5.5 ± 0.9
2	7	10.7 ± 1.2	7	7.7 ± 0.6	7	5.1 ± 1.4	7	5.3 ± 0.8	7	6.1 ± 0.9
4	7	9.4 ± 1.0	7	9.8 ± 0.9	7	7.6 ± 1.1	7	7.0 ± 0.6	7	6.1 ± 0.9
8	7	8.3 ± 0.9	7	7.6 ± 0.9	7	7.3 ± 1.0	7	6.8 ± 0.8	7	5.3 ± 0.8
12	6	7.2 ± 1.0	5	5.2 ± 0.7	2	7.2 ± 1.9	2	3.7 ± 2.1	2	3.4 ± 1.1

Table 2. Analysis of Variance (Hours 0 to 8)

Source of Variance	Sums of Squares	Degrees of Freedom	Mean Square	F	p
Hours	199.5	3	66.5	23.3	<0.001
Error	68.4	24	2.85		
Mode of Administration	351.9	4	87.9	13.3	<0.001
Hours x Mode	171.1	12	14.3	2.2	Not Significant
Error	634.9	96	6.6		

Table 3. Statistical Significance of Mean Values of Clinical Importance

Mode*	Hour**	F	p
IVQ 2 v IMQ	1	5.4	< 0.01
IMQ v Oral (Plain)	1	4.5	< 0.01
Oral (Plain) v Oral (Coated)	1	1.7	Not Significant
IVQ 4 v Oral (Coated)	4	2.6	< 0.05
IVQ 2 v Oral (Plain)	8	1.2	Not Significant
Oral (Coated) v IMQ	8	2.1	< 0.05

* IVQ 2 = Quinine infused in 2 hours
IVQ 4 = Quinine infused in 4 hours
IMQ = Intramuscular quinine
** Hour refers to number of hours elapsed since treatment begun

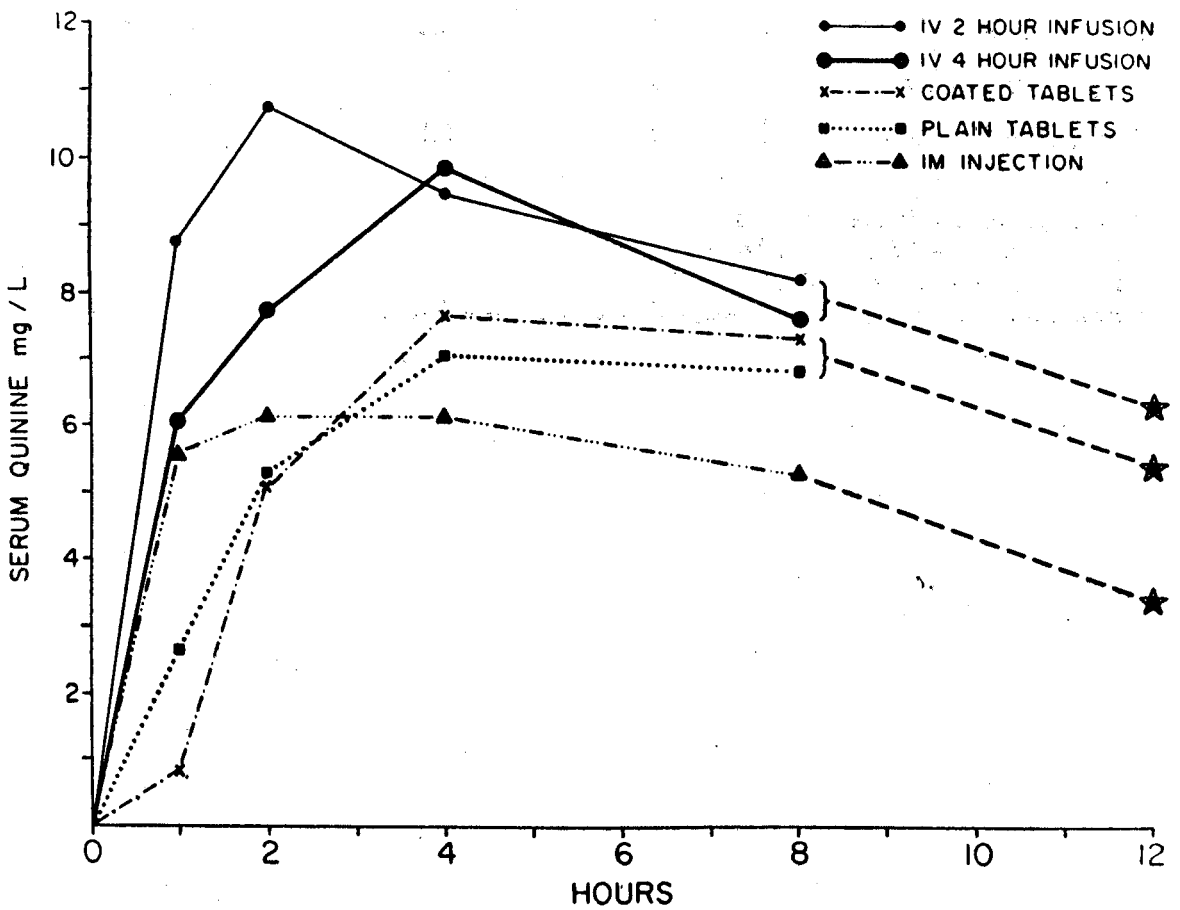

Figure I. Mean serum quinine concentrations following a single dose of quinine using 5 different modes of administration. There were 7 patients in each group. Complete data are not available at 12 hours.

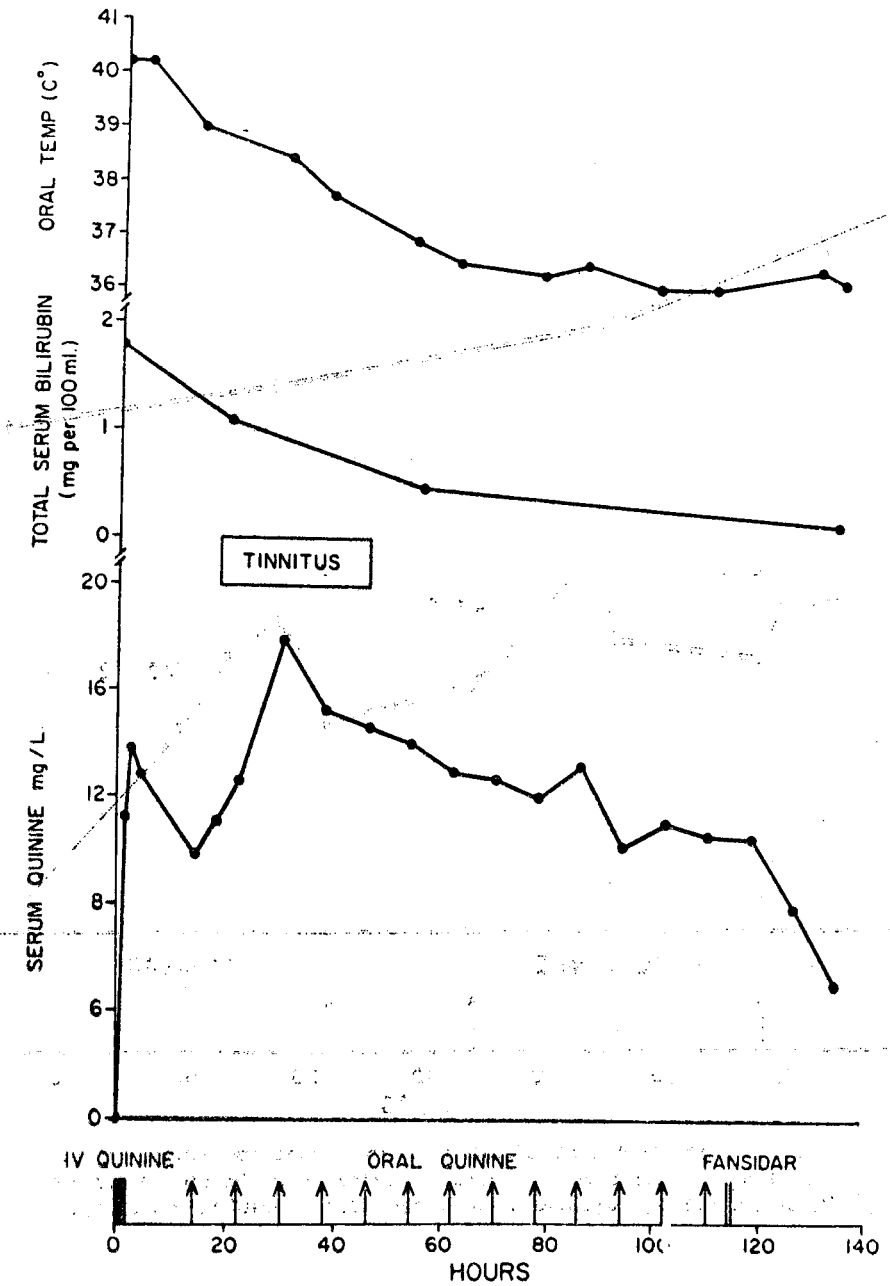

Figure 2. Routine quinine dose, 540 mg every 8 hours, produced a toxic serum concentration. There was a decrease in serum quinine despite constant dosage, associated with a decrease in total serum bilirubin,

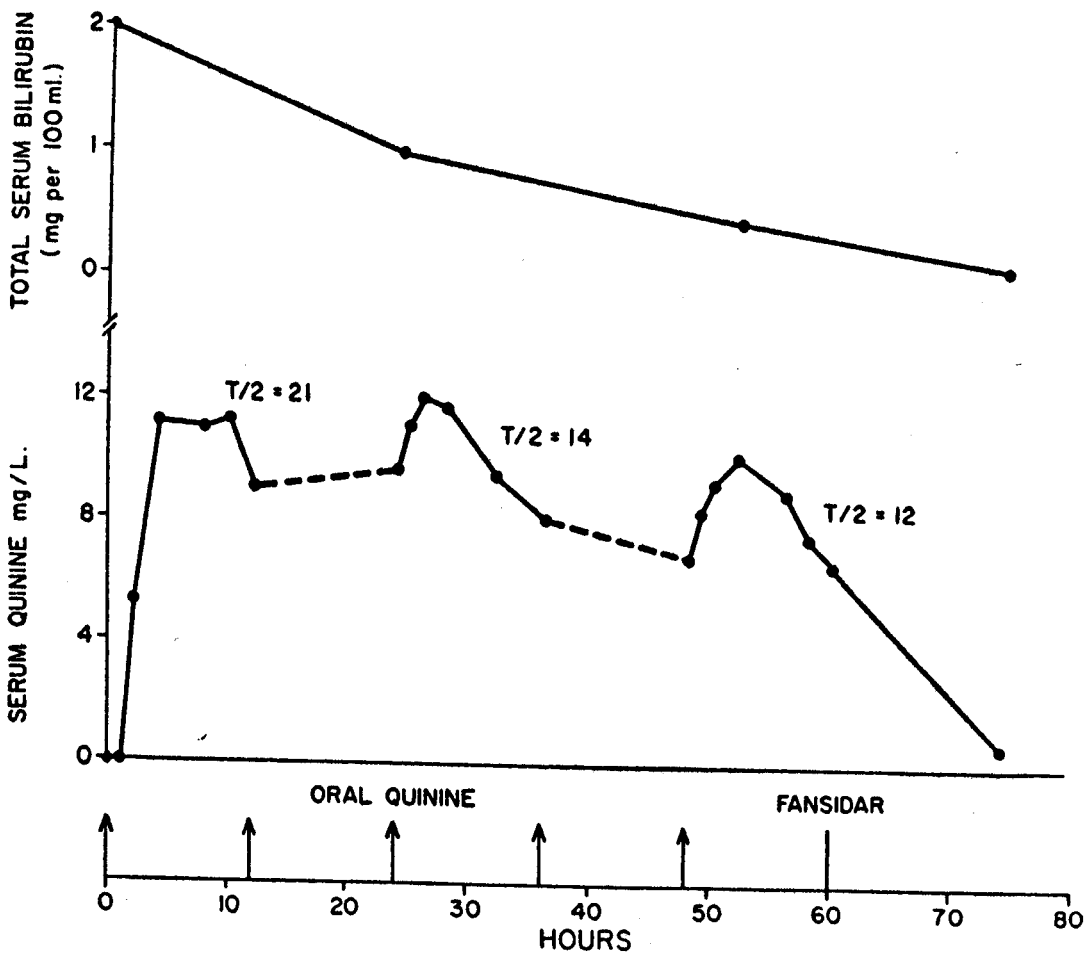

Figure 3. Clinical improvement and satisfactory serum quinine concentrations associated with 540 mg quinine every 12 hours. A decrease in the approximate half-life (T/2) of quinine was associated with decrease in total serum bilirubin.