Research from the South

High incidence of hypoglycaemia in African patients treated with intravenous quinine for severe malaria

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Abstract

Changes in plasma glucose and insulin concentrations were monitored over 24 hours in 28 African patients receiving quinine intravenously in an average dose of 8·5 mg base/kg over one hour eight hourly for severe malaria. The patients (nine children and 19 adults) were moderately undernourished; none was pregnant or had renal insufficiency. Plasma insulin concentrations rose during the infusion and then declined. Plasma glucose concentrations were decreased at two, three, and four hours after the start of the infusion. Insulin: glucose ratios were raised between half an hour and two hours after the start of the infusion. The three infusions of quinine increased plasma insulin concentrations in a similar way. In nine patients, including four children, plasma glucose concentrations fell below 2·8 mmol/l on one or two occasions. At the time of the hypoglycaemia plasma insulin concentrations were inappropriately high as shown by a consistent and often considerable increase in the insulin:glucose ratio.

Hypoglycaemia that may pass unnoticed in comatose patients is thus a common complication of treating severe malaria with quinine, in particular in children. Its high incidence calls for attentive monitoring and preventive measures.

Introduction

Hypoglycaemia has only recently been recognised as a potential complication of treating falciparum malaria with quinine.[1] Studies performed in Thailand showed that infusion of quinine intravenously in patients with cerebral malaria could precipitate severe hypoglycaemia, in particular in pregnant women.[1-3] This hypoglycaemia was partly ascribed to the stimulation of insulin release by quinine. Thus the ability of the drug to stimulate pancreatic β cells,[4-6] by a mechanism similar to that of hypoglycaemic sulphonylureas,[7] has been well established in vitro.

Malaria is endemic in equatorial Africa, where the incidence of chloroquine resistant *Plasmodium falciparum* is alarming.[8] Intravenous quinine is the only available treatment for the most severe cases. For several reasons we considered it important to compare the incidence of hypoglycaemia during such treatment in a rural hospital in Zaire with that reported from Thailand.[1,3] Firstly, the nutritional state of the population is not as good in the Kivu region of Zaire as it is in Thailand; secondly, the treatment regimens are different (in particular, no loading dose of quinine is given); and, thirdly, the previous studies did not include children who are said to have a lower incidence of hypoglycaemia than adults.[9]

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Patients and methods

The study was carried out at the Fomulac Hospital in Katana in the eastern Kivu region of Zaire. The study protocol was approved by the ethical committee of the Ministry of Public Health in Kinshasa. Relatives of the patients gave informed consent to investigation and treatment.

Thirty patients admitted consecutively to the intensive care unit for treatment of severe malaria entered the study. Patients presenting with severe haemolysis, haemoglobinuria, and renal insufficiency were not included as they were not treated with quinine. Two patients were excluded: one adult who was receiving a glucose infusion on arrival and one 3 year old boy who died an hour after admission (he had received unknown herbal remedies and on arrival had an extremely low plasma glucose concentration (0·45 mmol/l) and a relatively high insulin concentration (73 pmol/l)). The remaining 28 patients comprised nine children (four boys and five girls with an age range of 2½-10 years) and 19 adults (eight men and 11 women with an age range of 17-60 years). Six were conscious but could not tolerate oral treatment, three were lethargic, and 19 were unrousable. No patient showed signs of severe malnutrition but most were moderately undernourished: six of the nine children were below the third centile for height and weight,[10] and among the adults the body mass index, defined as weight (kg)/(height (m))^2 ranged from 15·6 to 23·0 (median 19). The median concentration of plasma proteins (and 95% confidence interval) was 72 (58 to 80) g/l in the children and 74 (66 to 80) g/l in the adults.[11] All the patients were acutely ill, gave histories of constant high fever, and showed asexual parasitaemia. In all the children and in four of the adults meningitis was excluded by examination of the cerebrospinal fluid.

Quinine dihydrochloride was infused intravenously over 60 minutes. For the adults 500 mg quinine salt (corresponding to an average of 8·5 mg quinine base/kg) was dissolved in 125 ml saline supplemented with 2·5% glucose. For the infants the dose was 10 mg quinine salt/kg (8·3 mg quinine base/kg) dissolved in 30 ml. During the following seven hours the solute was infused alone. The same regimen was repeated three times during the first 24 hours. On average adults and children received a total of 70 and 105 ml of fluid/kg/24 hours, respectively. Comatose patients regained consciousness 1·5-22·0 hours (median 3·5) after the start of the treatment. Two children and one adult were eating before completion of the study. Convulsions occurred in 11 patients and were treated with diazepam given intravenously, and the high fever in all the patients was treated by cooling and dipyrone given intramuscularly. Quinine was continued orally (25-30 mg quinine salt/kg/24 hours) for five days before the patients were discharged.

A heparinised Teflon catheter was inserted in a vein of the contralateral arm and left in place for blood sampling. Samples were taken at fixed times after the start of the treatment (0, ½, 1, 2, 3, 4, and 6 hours) as well as just before and one and three hours after the second and third infusions of quinine. The whole blood glucose concentration was estimated in each sample with a glucose oxidase indicator stick and a Dextrometer reading

system (Ames Co, Miles Laboratories). If the concentration was less than 2·8 mmol/l the speed of perfusion was increased (three patients) or a 20 ml bolus of hypertonic glucose (20%) was injected intravenously (six patients).

Plasma samples were stored at −25°C before being transported frozen to Belgium. Plasma glucose concentrations were measured by a glucose oxidase method (Glucose Analyzer, Beckman) and plasma insulin concentrations by a double antibody radioimmunoassay.[12] Plasma quinine concentrations were determined fluorimetrically after benzene extraction.[13]

Owing to the skewed distribution of many of the variables statistical analyses were made with non-parametric tests.[14,15] Results are expressed as medians with the range or 95% confidence interval for the median. The significance of changes in the variables during treatment was tested by Wilcoxon's signed ranks test for paired observations. The significance of differences in propositions between groups of patients was analysed by Wilcoxon's two sample test for unpaired observations. Probabilities of <0·05 were considered significant. The significance of an association between two variables was assessed by Spearman's rank correlation coefficient.

Results

On admission only two patients had detectable concentrations of quinine in their plasma (1·2 and 1·8 μmol/l). Table I shows that quinine concentrations reached a peak at the end of the infusion and then slowly declined. The peak concentration (median and 95% confidence intervals) was similar in the adults (16·3, 11·3 to 27·5 μmol/l) and the children (18·8, 8·8 to 30·0 μmol/l). Quinine infusions were associated with a rise in plasma insulin concentrations and a decrease in plasma glucose concentrations. The increase in plasma insulin concentrations occurred during the infusion, whereas the fall in plasma glucose concentrations was significant at two, three, and four hours after the start of the infusion. These changes resulted in an increase in the insulin: glucose ratio (table I). A weak correlation (r=0·56, p<0·01) was found between quinine and insulin concentrations at 30 minutes but not at 60 minutes (r=0·31). There was also no correlation (r=0·13) between the maximum increases in the concentrations of insulin and quinine.

TABLE I—*Changes in plasma quinine, insulin, and glucose concentrations and in insulin: glucose ratios induced by first quinine infusion (0-1 hour) in 28 patients with severe malaria; figures are medians (95% confidence intervals)*

Time (hours)	Plasma quinine (μmol/l)	Plasma glucose (mmol/l)	Plasma insulin (pmol/l)	Insulin: glucose ratio
0	0	5·0 (4·3 to 5·6)	82 (62 to 127)	15·9 (14·0 to 21·1)
½	11·3 (7·5 to 17·5)**	5·2 (4·6 to 5·6)	132 (89 to 188)**	22·7 (16·7 to 37·1)**
1	16·3 (12·5 to 26·3)**	5·0 (4·3 to 5·4)	116 (72 to 178)**	24·6 (18·1 to 32·7)**
2	Not done	3·6 (3·2 to 5·0)**	72 (62 to 120)	19·1 (14·4 to 32·3)*
3	13·8 (11·3 to 17·5)**	4·3 (3·1 to 5·2)**	68 (58 to 103)	16·0 (14·4 to 26·1)
4	Not done	4·6 (3·7 to 5·1)*	65 (55 to 75)	14·4 (12·5 to 18·7)
6	12·5 (10·0 to 15·0)**	4·8 (4·3 to 5·8)	62 (55 to 72)	13·3 (11·7 to 15·6)

* p<0·05, ** p<0·01 compared with value at time 0.

Table II shows that plasma concentrations of insulin and glucose and the insulin: glucose ratios were similar at the start of the three infusions of quinine, which consistently increased the concentration of insulin and the insulin: glucose ratio. Plasma glucose concentrations were not changed at the end of any of the quinine infusions. Three hours after the start of the second infusion, however, the median (95% confidence interval) plasma glucose concentration had decreased (p <0·01) from 5·2 (4·6 to 5·9) mmol/l to 4·4 (3·6 to 5·2) mmol/l. On the other hand, the rises in plasma insulin concentrations brought about by the third infusion of quinine were not followed by a significant fall in plasma glucose concentrations.

TABLE II—*Changes in plasma insulin and glucose concentrations and in insulin: glucose ratios induced by three successive quinine infusions in 28 patients with severe malaria; figures are medians (95% confidence intervals)*

Infusion period (hours)	Time of measurement	Plasma glucose (mmol/l)	Plasma insulin (pmol/l)	Insulin: glucose ratio
0-1	Before	5·0 (4·3 to 5·6)	82 (62 to 127)	15·9 (14·0 to 21·1)
	After	5·0 (4·3 to 5·4)	116 (72 to 178)	24·6 (18·1 to 32·7)
	Difference	−0·4 (−0·9 to 0)	24 (0 to 48)*	6·6 (1·3 to 12·9)*
8-9	Before	5·2 (4·6 to 5·9)	72 (65 to 89)	14·3 (11·5 to 17·7)
	After	4·7 (4·1 to 5·7)	120 (82 to 198)	24·7 (19·4 to 37·2)
	Difference	−0·2 (−0·7 to 0·1)	44 (14 to 65)*	8·1 (6·3 to 15·5)*
16-17	Before	4·8 (4·3 to 5·4)	68 (58 to 106)	16·4 (12·2 to 22·4)
	After	4·9 (4·4 to 5·6)	140 (82 to 226)	27·6 (20·0 to 45·8)
	Difference	−0·1 (−0·4 to 0·4)	62 (10 to 149)*	15·0 (3·5 to 23·5)*

*p <0·01.

The overall incidence of hypoglycaemia (plasma glucose concentration <2·8 mmol/l) was 32% (nine of 28 patients), but four of the nine children (44%) compared with five of the 19 adults (26%) became hypoglycaemic. Table III shows the clinical features of these nine patients. At the time of the hypoglycaemic episodes plasma insulin concentrations were higher than on admission in seven patients, and the insulin: glucose ratio was increased in all nine. Two children and one adult became hypoglycaemic on two occasions. The first, or only, hypoglycaemic episode occurred after the initial quinine infusion in seven of the nine patients.

On admission plasma glucose concentration (median and 95% confidence interval) was lower (p <0·01) in the nine patients who later developed hypoglycaemia (4·1, 3·8 to 4·9 mmol/l) than in the 19 other patients (5·4, 4·8 to 5·9 mmol/l). Plasma insulin concentrations and the insulin: glucose ratios were not significantly different. The peak plasma quinine concentrations and the plasma concentrations of proteins were similar in the two groups. There was also a large overlap in the maximum increase in insulin concentrations during the first eight hours in patients with hypoglycaemia (range 17-527 pmol/l, median 89) and without hypoglycaemia (range 0-243 pmol/l, median 44).

All patients recovered fully except one child, who had been hypoglycaemic and was left with some neurological deficit including dysphasia, paresthesia of the legs, and a hesitant walk.

Discussion

This study shows that hypoglycaemia is common in patients treated for cerebral malaria by intravenous infusion of quinine, in a regimen widely used in Zaire. The overall incidence (32%) was higher than in Thailand (8%).[1] Several factors could account for this difference. Firstly, our definition of hypoglycaemia (plasma glucose concentration <2·8 mmol/l) was less severe than that in the study from Thailand (<2·2 mmol/l, or <2·8 mmol/l with clinical symptoms). Our regular measurements of blood glucose concentration and the immediate correction of any fall below 2·8 mmol/l, however, probably prevented the development of more profound hypoglycaemia. In addition, mild hypoglycaemia is likely to escape detection if systematic sampling is not carried out. Secondly, quinine was infused more rapidly in our study (over one hour instead of four hours). We did not give a loading dose, however, and so the plasma quinine concentrations were not as high. Thirdly, in contrast to the Thai patients[1] our Zairian patients were often moderately undernourished. This may have affected the efficacy of the insulin and of the counterregulatory mechanisms normally brought into operation to maintain glucose homoeostasis, particularly in children.[16]

In the whole group of patients a highly significant increase in plasma insulin concentration accompanied the infusion of quinine and was followed by a fall in the plasma glucose concentration. When hypoglycaemia occurred the plasma insulin concentration was still increased and was inappropriately high for the low glucose concentrations. These observations are in keeping with those made in Thailand,[1,3] and from this evidence and the fact that quinine has a direct stimulatory effect on β cells[4-7] we conclude that the stimulation of insulin release by quinine contributes to the hypoglycaemia of patients with malaria. The lack of a correlation between the maximum increases in plasma insulin and quinine concentrations does not invalidate this conclusion. Thus the insulinotropic action of a fixed concentration of quinine depends on the existing concentration of glucose in vitro.[6] In addition, small differences in quinine binding by plasma proteins[17] may influence the response of β cells because the concentration of free quinine (about 10%) is close to the threshold concentration for increasing insulin release.[4]

Though quinine may occasionally cause hypoglycaemia in other types of patients,[18] it has no such effect in normal volunteers[1] or in rats,[19] in spite of a rise in plasma insulin concentrations. Other factors such as increased metabolic demands or reduced effectiveness

TABLE III—*Clinical features of the patients with hypoglycaemia*

Case No	Sex and age (years)	Height (cm)	Weight (kg)	Nutritional state (children = centile; adults = body mass index)	Coma grade on admission*	Time of hypoglycaemia after admission (hours)	On admission: Plasma glucose (mmol/l)	On admission: Plasma insulin (pmol/l)	On admission: Insulin: glucose ratio	During hypoglycaemic episode: Plasma glucose (mmol/l)	During hypoglycaemic episode: Plasma insulin (pmol/l)	During hypoglycaemic episode: Insulin: glucose ratio
1	M, 6	99	12	< third	2	4†	3·8	72	18·9	1·0	86	86·0
2	F, 6	105	13	< third	2	2†	4·1	44	10·7	2·5	294	118
3	F, 7	109	16	< third	2	24	4·2	68	16·2	1·7	51	30·0
4	F, 10	150	32	50th	2	11	3·9	82	21·0	2·1	68	32·4
5	F, 19	156	56	23	2	3	5·1	161	31·6	2·7	171	63·3
6	F, 20	156	52	21	2	3	4·3	65	15·1	2·5	67	26·8
7	M, 34	170	54	19	0	2†	3·3	55	16·7	2·1	321	153
8	F, 39	159	46	18	1	1	3·9	109	27·9	2·6	198	76·2
9	M, 60	168	54	19	0	2	4·9	127	25·9	2·7	215	79·6
Median							4·1	72	18·9	2·5††	171‡	76·2††
Confidence intervals							3·8 to 4·9	55 to 127	15·1 to 27·9	1·7 to 2·7	67 to 294	30 to 118

*0 Conscious; 1 = lethargic; 2 = unrousable.
†Had two hypoglycaemic episodes.
‡ $p < 0·10$, †† $p < 0·01$ Compared with values on admission.

of glucose counterregulatory mechanisms may also play a part in the effect in patients with severe malaria. In a recent prospective study performed in Gambia one third of the children with severe malaria were hypoglycaemic on admission to hospital.[20] This hypoglycaemia was not due to hyperinsulinaemia and was ascribed to a deficit in glucose production. In our study only one child out of 10 was hypoglycaemic on arrival in hospital, but this confirms other evidence that hypoglycaemia may occur in the absence of quinine treatment, indicating the multifactorial origin of the disorder in patients with malaria.[3 21 22]

Pregnant women are prone to develop hypoglycaemia during quinine infusion[1-3]; this study shows that children incur the same high risk. The only predictive factor that we could identify was lower plasma glucose concentrations on admission in those patients who subsequently developed hypoglycaemia.

Though all the patients had severe malaria and two thirds of them had cerebral malaria according to the latest diagnostic criteria,[9] only one died (before treatment was started). This low mortality may be due to the fact that we excluded patients with renal insufficiency or associated complications from our series, and also to the high sensitivity of the parasite to quinine in the region.[8] Our comatose patients all regained consciousness much sooner than those reported in studies from Thailand.[23]

In conclusion, hypoglycaemia often complicates the intravenous administration of quinine for the treatment of severe malaria. Pregnant women, children, and those patients whose blood glucose concentration is already fairly low on admission are at particular risk. This complication should not, however, discredit an efficient treatment; the use of saline supplemented with 10% glucose (currently adopted in this hospital) and, if possible, monitoring with glucose oxidase sticks may effectively reduce its occurrence and severity.

We thank the staff of the intensive care unit of the hospital. This study was supported by funds from the Administration Générale de la Coopération au Développement, Brussels, of which WO is a research fellow. JCH is head of research of the Fonds National de la Recherche Scientifique Brussels.

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(Accepted 10 July 1987)