Research from the South

Hypoglycaemia and antimalarial drugs: quinidine and release of insulin

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Abstract

Life threatening hypoglycaemia has been closely associated with the use of quinine, but the effect of quinidine and the synthetic antimalarials on the homoeostasis of glucose has not been investigated. In volunteers given a fixed dose of 500 mg base and patients with malaria given a quinidine loading dose (15 mg base/kg) mean (SEM) plasma insulin concentrations rose from 6·1 (1·5) mU/l to 10·9 (4·4) mU/l ($p<0·02$) and 10·4 (2·0) mU/l to 18·5 (5·3) mU/l ($p<0·04$), respectively. Plasma glucose concentrations fell from 4·5 (1·1) mmol/l (81 (20) mg/100 ml) to 4·0 (0·3) mmol/l (72 (5) mg/100 ml) in volunteers ($p<0·04$) and from 5·7 (1·3) mmol/l (102 (23) mg/100 ml) to 4·8 (1·6) mmol/l (86 (29) mg/100 ml) in patients ($p<0·05$). One of two patients with cerebral malaria and acute renal failure became profoundly hypoglycaemic (plasma glucose concentration 1·4 mmol/l (25 mg/100 ml), plasma insulin concentration 3·1 mU/l).

Hypoglycaemia may occur in any severely ill fasting patient given parenteral quinidine. The other antimalarials tested, chloroquine, amodiaquine, mefloquine, and halofantrine, did not stimulate the release of insulin, an important advantage that should be taken into account when treatment is chosen for Plasmodium falciparum malaria.

Introduction

Cinchona bark and the alkaloids extracted from it have been used for over 300 years. When the bark was introduced into Europe physicians disagreed about dosage and toxicity,[1] and these issues have been controversial ever since. Cinchonism, a group of symptoms including dizziness, tinnitus, deafness, nausea, and vomiting, was a well known side effect, but in 1891 Laveran concluded that the main danger from quinine treatment was cardiac depression.[2] In 1925 Hughes showed that quinine could lower the blood sugar concentration,[3] but these findings were soon forgotten.

Recently, hyperinsulinaemic hypoglycaemia was linked to the use of quinine in the treatment of falciparum malaria.[4] This important, life threatening complication may be missed, however, if severe neuroglycopenic signs are wrongly attributed to cerebral or other multisystem disorders. In developed countries parenteral quinidine, recently revived for both its antiarrhythmic[5,6] and antimalarial[7] action, is often given to severely ill patients in whom hypoglycaemia might be obscured by underlying disease.

For these reasons we investigated the effect of antimalarial drugs, including quinidine, on the homoeostasis of glucose in volunteers and patients with falciparum malaria.

Patients and methods

Our studies, which were approved by the ethical committee of the faculty of tropical medicine, Mahidol University, Bangkok, were carried out during pharmacokinetic and therapeutic trials of antimalarial drugs (unpublished findings).[7-9]

VOLUNTEERS

Adult Thai volunteers whose body weights (range 41-61 kg, mean 49 kg) were within the normal range for age, sex, and height, who had no evidence of protein or energy malnutrition, and who gave fully informed consent fasted overnight for over eight hours. Six volunteers were given chloroquine phosphate (Bayer) 3 mg base/kg body weight intravenously over 10 minutes; seven oral mefloquine (Roche, Basle) 750 mg base suspended in 100-200 ml deionised water; nine oral halofantrine hydrochloride (WR171669, lot number WRA-1-D3181) 1000 mg salt as capsules with 100 ml water; and eight quinidine gluconate (Eli Lilly) 500 mg base dissolved in 250 ml 0·9% saline infused intravenously over 60 minutes.

PATIENTS WITH FALCIPARUM MALARIA

Amodiaquine dihydrochloride 10 mg base/kg body weight was dissolved in 250 ml 0·9% saline and infused intravenously over four hours in seven patients (weight range 34-60 kg, mean 48 kg) who were acutely ill with a history of fever lasting 24-68 hours (asexual parasitaemia ranging from 6336 to 268 891 trophozoites/μl) and who had not eaten on the day of admission to hospital. Quinidine gluconate (Eli Lilly) 15 mg base/kg body weight was dissolved in 250 ml 0·9% saline and infused over four hours in 10 patients (weight range 39-51 kg, mean 48 kg) with severe malaria (parasitaemia 66 971-1 736 106 trophozoites/μl), including two in coma and acute renal failure.

Blood samples, taken through an indwelling heparinised polytetrafluoroethylene (Teflon) catheter inserted into an antecubital vein, were dispensed into plastic heparin tubes and spun immediately in a chilled centrifuge. Plasma samples were separated and frozen immediately and stored at −70°C or below in Bangkok and Oxford until they were analysed. Samples were transported to the United Kingdom on dry ice. Concentrations of glucose

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were measured by the hexokinase method, insulin by immunoassay with charcoal-phase separation[10] after precipitation of proteins with polyethylene glycol (coefficient of variation: interassay 10-12%, intra-assay 17%), quinidine by the benzene extraction fluorescence method,[11] and chloroquine and amodiaquine by high performance liquid chromatography using methods published previously.[9 12]

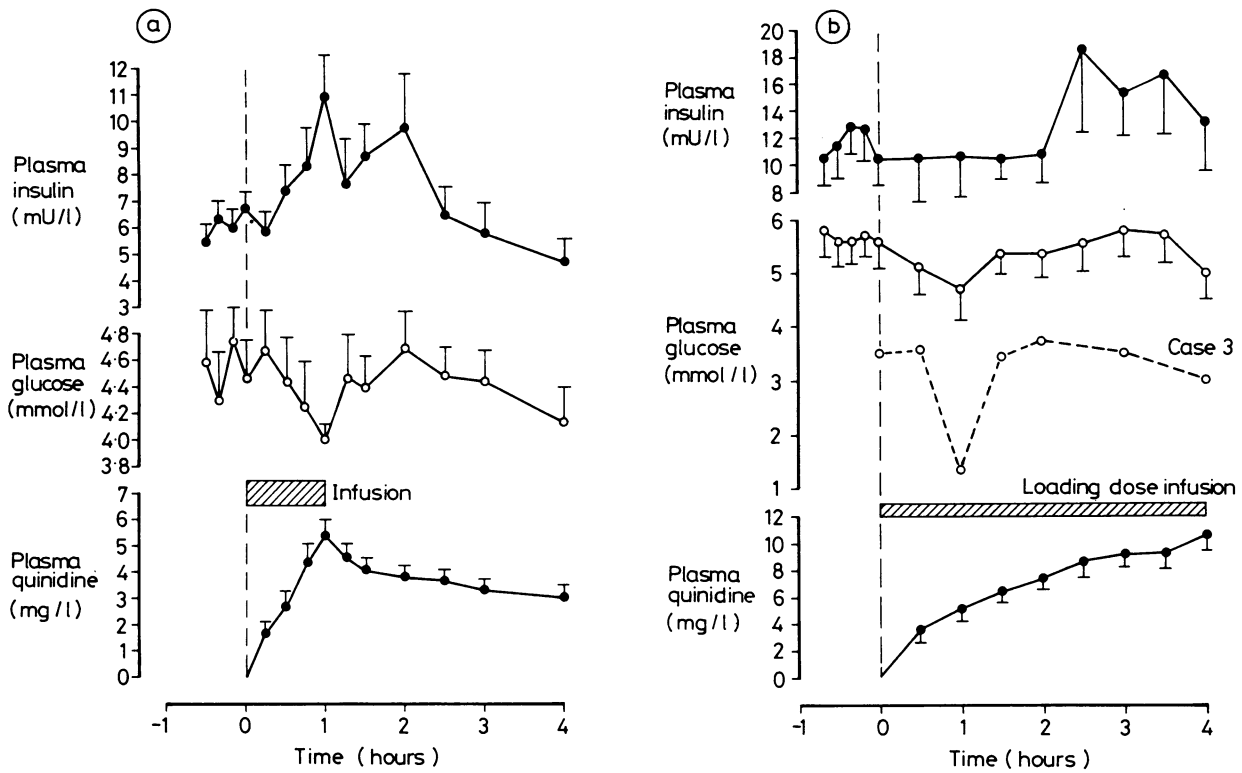
STATISTICAL METHODS

Glucose and insulin concentrations at different time intervals were analysed by comparison of means.

Results

In volunteers mean (SEM) quinidine concentrations rose to a peak of 5·4 (1·8) mg/l, plasma insulin concentrations rose from 6·1 (1·5) mU/l to 10·9 (4·4) mU/l ($p<0·02$), and plasma glucose concentrations fell from 4·5 (1·1) mmol/l (81 (20) mg/100 ml) to 4·0 (0·3) mmol/l (72 (5) mg/100 ml) ($p<0·04$; figure (a)). Peak plasma chloroquine concentrations after the injection were 784-6649 ng/ml (mean 2913 ng/ml). (Mefloquine and halofantrine concentrations were not measured.) There was no significant change in plasma insulin or glucose concentrations in volunteers treated with mefloquine, halofantrine, or chloroquine (table).

In patients with malaria mean (SEM) quinidine concentrations rose to a peak of 10·9 (1·1) mg/l and there was a significant rise in plasma insulin concentration from a baseline of 10·4 (2·9) to 18·5 (5·3) mU/l 2·5 hours after starting treatment with quinidine ($p<0·04$). During the first hour mean plasma glucose concentration fell significantly from 5·7 (1·3) mmol/l (102 (23) mg/100 ml) to 4·8 (1·6) mmol/l (86 (29) mg/100 ml) ($p<0·05$) in patients treated with quinidine (figure (b)). One of two patients with cerebral malaria and acute renal failure (case 3) became hypoglycaemic (plasma glucose concentration 1·4 mmol/l (25 mg/100 ml)) when the plasma quinidine concentration was 6·0 mg/l. In this patient plasma insulin concentrations ranged from 3·1 to 9·0 mU/l while receiving the quinidine loading dose. Plasma amodiaquine concentrations at the end of the infusion were 82-820 ng/ml (mean 394 ng/ml). There was no significant change in concentrations of plasma glucose or insulin in the patients with malaria given amodiaquine (table).



Plasma insulin, glucose, and quinidine concentrations in (*a*) eight fasting volunteers given quinidine as a fixed dose of 500 mg base infused intravenously over one hour, and (*b*) 10 patients with severe falciparum malaria given quinidine as a loading dose (15 mg base/kg body weight) infused over four hours. Plasma insulin concentrations increased significantly one hour after starting the fixed dose ($p<0·02$) and 2·5 hours after the loading dose ($p<0·04$). At one hour plasma glucose concentration fell significantly in volunteers ($p<0·04$) and patients ($p<0·05$). Values are means (SEM).
Conversion: SI to traditional units—Glucose: 1 mmol/l≈18 mg/100 ml.

Plasma glucose (mmol/l) and insulin (mU/l) concentrations after antimalarial treatment. Values are means (SEM)

Treatment	Concentrations	Time before treatment (minutes) 30	20	10	Time after starting treatment (minutes) 0	15	30	45	60	75	90	120	150	180	240
Mefloquine (n=7)	Glucose	4·1 (0·2)	4·2 (0·2)	4·3 (0·2)	4·2 (0·2)	4·3 (0·2)	4·2 (0·2)	4·2 (0·3)	4·3 (0·2)	3·9 (0·2)	4·1 (0·2)	4·8 (0·5)	4·7 (0·5)	4·3 (0·4)	4·1 (0·2)
	Insulin	7·1 (2·7)	7·3 (3·6)	7·6 (5·0)	8·5 (5·8)	7·9 (3·6)	5·8 (2·6)	5·1 (1·1)	4·6 (1·5)	3·9 (1·6)	5·1 (1·8)	4·1 (2·1)	4·6 (1·1)	4·7 (2·0)	3·4 (1·2)
Halofantrine (n=9)	Glucose	4·9 (0·1)	5·0 (0·1)	4·2 (0·2)	4·9 (0·1)	4·9 (0·1)	4·9 (0·1)	4·9 (0·1)	4·8 (0·4)	4·9 (0·1)	4·8 (0·4)	4·7 (0·1)	4·9 (0·1)	4·7 (0·1)	4·9 (0·1)
	Insulin	6·9 (1·6)	8·8 (2·2)	7·5 (1·5)	6·3 (1·2)	6·9 (1·4)	5·4 (1·6)	7·0 (1·5)	6·9 (1·2)	6·4 (1·0)	6·3 (1·4)	4·8 (1·1)	3·5 (1·1)	3·9 (0·9)	4·2 (0·9)
Amodiaquine (n=7)	Glucose		5·8 (0·8)	5·9 (0·4)	5·3 (0·4)				5·5 (0·5)			5·6 (0·7)		5·4 (0·7)	5·7 (0·4)
	Insulin		28·0 (16)	21·0 (6·9)	13·0 (4·6)				11·1 (2·3)			11·0 (2·6)		13·7 (5·4)	16·5 (7·5)
Chloroquine (n=6)	Glucose	4·7 (0·6)	5·0 (0·5)	4·8 (0·4)	4·4 (0·2)	4·5 (0·4)	4·5 (0·4)	4·8 (0·5)	5·4 (0·8)		5·7 (1·3)	5·1 (1·4)			
	Insulin	17·2 (4·8)	19·7 (5·1)	17·4 (5·2)	16·6 (5·0)	15·9 (5·5)	19·7 (7·4)	19·7 (7·4)	17·3 (10·6)		24·3 (10·1)	22·2 (11·6)			

Conversion: SI to traditional units—Glucose: 1 mmol/l≈18 mg/100 ml.

Discussion

Substantial clinical and laboratory evidence has shown that quinine stimulates β cell secretion of insulin (unpublished findings).[4 13 14] In volunteers given intravenous quinine the increase in plasma insulin concentration depresses plasma glucose concentration,[4] but in patients with malaria virtually intractable hypoglycaemia may occur owing to sustained hyperinsulinaemia. Quinidine, but not the synthetic antimalarials, should be regarded as having similar potential. In healthy subjects the disturbance in glucose homoeostasis induced by quinidine will probably be antagonised effectively by a counter-regulatory increase in the concentrations of cortisol, glucagon, growth hormone, and catecholamines, but by analogy with quinine treatment hypoglycaemia may occur in fasting patients in whom homoeostasis is impaired. The risk, however, is unpredictable. Is hypoglycaemia responsible for some of the toxicity attributed to the cinchona alkaloids or the underlying disease for which they have been given?

Apprehension, confusion, blurred vision, vertigo, fitting, and coma are common conditions after an overdose of quinine and quinidine,[15-18] but none of three recent studies comprising 229 cases mentioned exclusion of hypoglycaemia.[17-19] Signs of hypoglycaemia are non-specific, though in comatose patients features of decortication, decerebration, and focal neurological abnormalities may be useful clues.[20] Glucagon has a positive inotropic action on the heart,[21] but its beneficial effect in cases of quinidine overdose may be caused by the reversal of hypoglycaemia.[22]

In patients with malaria treated with quinidine the plasma glucose concentration fell while the plasma insulin concentration remained unchanged, a homoeostatic defect reminiscent of that seen in patients with insulinomas.[23] When these patients fast peripheral vein insulin concentrations may not be raised in absolute terms, but the prevailing insulin concentration is inappropriate and fails to fall in response to decreases in plasma glucose concentration.[23] Mismatching of glucose and insulin concentrations aggravates hypoglycaemia as output of hepatic glucose is sensitive to inhibition by insulin.[24] The action of quinidine on the β cell seems to be the most probable cause of this disturbance. Plasma insulin concentrations rose and plasma glucose concentrations fell significantly when plasma quinidine concentrations exceeded 8 mg/l in patients with malaria and 5 mg/l in control subjects, whereas no changes were seen in those given other drugs. Quinidine, like quinine, is a potent stimulus for the release of insulin in vitro (I Atwater, personal communication). Fever and its associated pathophysiology, in addition to the parasite itself, create further demands on the glucose supply and may precipitate hypoglycaemia in patients with glucose-insulin mismatching. Failure of glucose counter-regulatory mechanisms may also cause hypoglycaemia, though this response appears adequate in patients with malaria (unpublished findings).

Quinidine is more likely to cause hypoglycaemia in children,[25] pregnant women,[24] and those with renal failure.[26] Some subjects become hypoglycaemic after single nocturnal doses of quinine[27]; as quinidine may have the same effect hypoglycaemia should be excluded as a cause of unexplained symptoms even in patients taking small oral doses.

Neither chloroquine nor any other synthetic antimalarial tested stimulated insulin release or altered glucose homoeostasis acutely. This important advantage should be considered before quinine is advocated as the sole drug suitable for the parenteral treatment of severe malaria.[28] Quinidine may cause or aggravate hypoglycaemia and thus offers no advantage over quinine from this point of view; new drugs are urgently needed. One approach will be to screen analogues of the cinchona alkaloids in which structural differences prevent the triggering of insulin release but which none the less retain antimalarial activity (E H D Smit and others, personal communication).

This study and others of patients from Zambia,[29] Irian Jaya (S L Hoffman, personal communication), the Gambia (K Marsh, personal communication), Tanzania,[30] and Thailand[13] show that insulin release stimulated by quinine cannot be the only cause of malarial hypoglycaemia. Other mechanisms, including the action of the parasite and its products, must be investigated.

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