Antimalarial drugs and glucose metabolism

T. M. E. Davis
University of Western Australia, Department of Medicine, Fremantle Hospital, Fremantle, Western Australia

Keywords: antimalarial drugs, hypoglycaemia, glucose, insulin

Introduction
A number of the drugs used as prophylaxis against, or treatment for, malaria have clinically significant metabolic side-effects. Of these, hypoglycaemia resulting from quinine administration is one of the most important [1]. Quinidine, the diastereoisomer of quinine, can also cause this complication [2]. The 4-aminoquinoline chloroquine is known to influence glucose metabolism in ways which could lead to low blood glucose concentrations [3, 4], although reports of chloroquine-treated patients with acute malaria who have developed hypoglycaemia are rare [5]. Recently, the quinoline methanol mefloquine has been shown to reduce plasma glucose concentrations during a conventional prophylactic course in healthy young adults [6]. In all these situations, raised serum or plasma insulin concentrations have been observed.

The maintenance of appropriate plasma glucose concentrations in both basal and fed states is largely a function of the action of insulin. Counter-regulatory hormones, especially glucagon, become important only when the plasma glucose starts to fall below normal. However, increased catecholamine and cortisol secretion in the absence of hypoglycaemia occurs in stress situations including infections. Other factors such as increased plasma free fatty acid concentrations and ketonaemia may also contribute to a raised basal plasma glucose. However, continued host and parasite glucose demand, impaired hepatic glycogenolysis and gluconeogenesis, cytokine effects and the inability of the patient to take sufficient carbohydrate by mouth because of nausea and vomiting increase the propensity to hypoglycaemia in malaria [1]. The added influence of hyperinsulinaemia due to antimalarial treatment can result in severe, refractory hypoglycaemia with serious neurological and other sequelae if it remains undetected or inadequately treated.

Several questions arise concerning the effect of antimalarial drugs on plasma glucose and insulin concentrations. Which drugs have the greatest effect on insulin secretion and why? Is this effect related to the total or free (unbound) plasma concentration of the drug? Is there synergism between antimalarial drugs of the same or different classes? Do the drugs have other effects on glucose metabolism which could contribute to hypoglycaemia? Are there special situations, during either prophylactic or treatment courses, in which drug effects on glucose metabolism are exaggerated or, conversely, attenuated? Do specific effects suggest novel ways of preventing or treating hypoglycaemia? The published data relating to these questions will be assessed in the present review including, where possible, their reanalysis or reinterpretaion in the light of the current understanding of mechanisms governing glucose homoeostasis in humans.

Techniques for evaluation of glucose metabolism in humans
An accurate and promptly-available blood or plasma glucose concentration may, on its own, be very useful clinically but is a limited measure of glucose tolerance in a patient with a disease such as malaria. The measurement of serum insulin in addition to glucose gives improved but still relatively crude information regarding complex, non-linear feedback between the pancreas and tissues which produce or utilise glucose. Because of this situation, a number of physiological tests and associated mathematical models have been developed which allow a better characterisation of factors which regulate plasma glucose in humans.

Amongst the most technically demanding and labour intensive are ‘clamp’ studies in which the plasma glucose concentration, and also the serum insulin if necessary, can be maintained or ‘clamped’ at predetermined levels through the simultaneous intravenous infusion of dextrose and insulin at rates which are calculated from the results of frequent bedside plasma glucose sampling. Conventional clamp studies are, however, concerned primarily with the direct estimation of insulin sensitivity (for which they are regarded as the reference method) rather than insulin secretory capacity [7], though hyperglycaemic clamps have been recently highlighted as an underutilised tool for assessment of beta cell responsiveness [8].

In an attempt to simplify the testing process but still provide robust estimates of pancreatic beta cell secretory capacity and its effect on tissue glucose uptake, two other approaches have been developed which provide results consistent with those of clamp studies. The first is based on the ‘minimal model’, which is a compartmental analysis of plasma glucose and insulin concentrations during a frequently-sampled intravenous glucose tolerance test (FSIVGTT) [9]. Estimates of insulin sensitivity ($\text{SI}$), glucose effectiveness ($\text{SG}$) and pancreatic responsiveness ($\text{w}_1$ and $\text{w}_2$) are generated [10]. The minimal model has been used effectively to assess aspects of glucose tolerance in a variety of different physiological situations and disease states [11].

The second approach is that which underlies Homoeostasis Model Assessment (HOMA) and Continuous Infusion of Glucose with Model Assessment (CIGMA). HOMA is applied in the fasting or post-absorptive state [12] and CIGMA involves standardised dextrose administration over an hour to achieve a suprabasal but still physiological plasma glucose concentration [13]. These analyses are based on a structural computer model of the insulin-glucose feedback system which incorporates a mathematical description of the function of organs involved in regulation of plasma glucose.

Correspondence: Professor T. M. E. Davis, University of Western Australia, Department of Medicine, Fremantle Hospital, PO Box 480, Fremantle 6160, Western Australia.
The model uses basal (HOMA) or achieved (CIGMA) plasma glucose and insulin concentrations to provide values of beta cell function (%B) and insulin sensitivity (%S) expressed in terms of those in a sample of healthy, non-diabetic Caucasian volunteers with an arbitrary mean of 100% and a logarithmic distribution for both variables.

Quinine and quinidine

The cinchona alkaloids are known to increase insulin secretion by blocking ATP-sensitive potassium (K\text{ATP}) channels in pancreatic beta cells [14], a property shared with the sulphonylurea drugs used in the treatment of non-insulin-dependent diabetes mellitus (NIDDM) [15]. Though other host and parasite-specific factors contribute to hypoglycaemia in falciparum malaria, quinine-associated hyperglycaemia has been reported consistently in series of adult, paediatric and pregnant patients from a variety of endemic areas [16–19]. Hypoglycaemia during quinidine treatment has also been reported, though much less often [2]. This could be because it has less antimalarial use than quinine on a world scale but, interestingly, reports of hypoglycaemia in patients receiving quinidine as an antihypertensive drug have also been rare [20].

Studies of quinine and quinidine in healthy volunteers allow an examination of their comparative metabolic effects without the confounding influence of malaria per se. In a study of 11 young Thai adults [21], each subject had a 2-h intravenous dextrose infusion according to an extended CIGMA protocol on three occasions separated by at least a week. On each occasion, normal saline, quinine or quinidine was infused together with the dextrose over the second hour. The order of these parallel infusions was random. Both alkaloids were given at a dose of 10 mg base kg\textsuperscript{-1} body weight. Analysis using CIGMA was not attempted beyond 1 h data in the original report [21]. Drug-related effects on glucose metabolism were inferred from changes in serum insulin alone.

Recently, the CIGMA model has been extended to provide estimates of beta cell function and insulin sensitivity at the end of a 2 h dextrose infusion [22, 23]. A summary of reanalysis of the original volunteer data [21] using this approach is shown in Figure 1. In the case of the normal saline control infusion, CIGMA estimates of %B after 1 and 2 h were, as expected, similar. Quinine infusion was associated with an average relative 330% increase in %B over the second hour. In the case of quinidine, the equivalent increase in %B was much less (40%) but still statistically significant. Thus, therapeutic doses of quinine have a more potent effect on the pancreatic beta cell than the same doses of quinidine, an observation which might account for the apparently greater tendency for quinine to cause hypoglycaemia in clinical practice.

When the ratio of %B after the second to that after the first hour (before and after drug) is plotted against total plasma drug concentration (see Figure 2), there appears to be a log-linear relationship with a y-intercept near that of the normal saline control study (a ratio close to 1.0). This could be interpreted as showing that quinine and quinidine share the same dose-beta cell response relationship but that pharmacokinetic differences account for the discrepancy shown in Figure 1. This hypothesis is, however, not supported by plasma concentrations of free (unbound) drug (see Figure 3). As free concentrations in plasma may be a better surrogate marker of tissue drug levels than total, variables such as the binding of each diastereoisomer to beta cell K\text{ATP} channels could determine the apparent pharmacodynamic difference between these closely related compounds. A stereoisomer-specific response is also seen in other tissues [24].

Beta cell function might be influenced by malaria per se as well as treatment in ways which could invalidate the extrapolation of findings in healthy volunteers to acute illness. In a study of 10 Thai adults with uncomplicated falciparum malaria treated initially with intravenous quinine [25], the same prolonged CIGMA protocol was followed in both acute illness and early convalescence. Reanalysis of the original plasma glucose and insulin concentrations at 1 and
Antimalarial drugs and glucose metabolism

Figure 2 Ratio of beta cell function (%B) from CIGMA (quinine (●) and quinidine (■)) or HOMA (mefloquine, (▲)) analysis before and after drug administration plotted against total plasma drug concentration. Data are mean ± s.d. for both ratio and drug concentration. The solid line indicates the line of best fit using pooled quinine and quinidine data.

Figure 3 Ratio of beta cell function (%B) from CIGMA (quinine (●) and quinidine (■)) analysis before and after drug administration plotted against plasma concentration of free drug. Data are mean ± s.d. for both ratio and drug concentration.

2 h is summarized in Figure 4. Geometric mean %B values at 1 and 2 h at presentation were similar to those at the same times in convalescence, implying that non-severe malaria does not alter beta cell function significantly. However, %B after quinine administration was significantly less in both acute illness and convalescence compared with values in healthy Thai volunteers of similar age (see Figure 4).

This observation suggests that the beta cell response to the combined stimulus of glucose and quinine is depressed during acute malaria and for a period of weeks after parasite clearance. In a study of patients with severe malaria in whom a modified FSIVGTT was performed [26], peak serum insulin concentrations after intravenous glucose (60 g) response) were not augmented by quinine pre-treatment. Thus it appears that malaria has little effect on insulin secretion at near basal levels but that it is associated with a depressed response at greater levels of beta cell stimulation. If anything, this would protect against hyperinsulinaemic hypoglycaemia in quinine-treated patients but such an effect may be of minor clinical importance.

In a sample of gliclazide-treated patients with NIDDM, 600 mg quinine sulphate produced a mean fall in plasma glucose of approximately 1.0 mmol l\(^{-1}\) at peak plasma quinine compared with the plasma glucose profile when no quinine was taken [27]. A similar change was observed in a matched group of non-diabetic controls who took quinine and no drug respectively on the two test days. In the patients with NIDDM, the insulin response to the combination of quinine and gliclazide did not suggest synergism. These results indicate that combination antimalarial regimens such as quinine, quinidine and cinchonine [28], or quinine given to a patient on failed mefloquine prophylaxis, will not greatly increase the risk of hypoglycaemia compared with treatment doses of individual drugs. Compounds such as diazoxide which activate the K\(^+\) ATP channel may reverse hyperinsulinaemia due to cinchona alkaloids provided that they have no other unfavourable effects. In the case of diazoxide [15], its hypotensive action would appear to limit clinical use.

In a recently-published large-scale comparative trial of quinine and artemether in Vietnamese adults with severe falciparum malaria [29], hypoglycaemia occurred in 25% of quinine-treated patients compared with 11% of those allocated artemether. These data confirm that hypoglycaemia is a common complication of severe malaria and that quinine significantly increases its occurrence. The main result of the trial was that the two drugs were associated with similar mortality rates despite concerns of emerging resistance to quinine. This suggests that quinine will remain a first-line drug for malaria in tropical and other countries.

Chloroquine

In a study of six healthy volunteers and six patients with NIDDM [3], it was concluded that a short course of...
chloroquine did not affect overall glucose tolerance in the controls but that there was an improvement in diabetic subjects. Nevertheless, there was a statistically significant (P<0.01) reduction in fasting plasma glucose after chloroquine in the non-diabetic subjects. No individual values or summary data were reported but, as estimated from graphed mean curves, chloroquine produced an average 0.7 mmol l^{-1} fall in basal plasma glucose which is of the order of that associated with prophylactic doses of mefloquine in young adults [6]. In addition, the mean basal plasma insulin was greater after chloroquine than before even if this did not achieve statistical significance. HOMA analysis of mean fasting plasma glucose and insulin data before and after chloroquine displayed in graphical form [3] suggests that beta cell function is increased by a proportion similar to that in Thai volunteers who received intravenous quinidine (approximately 30%) [21]. From the results of in vitro experiments (P. Smith, University of Oxford, unpublished observations), this effect is, as in the case of the cinchona alkaloids, likely to be mediated through K⁺-ATP channel blockade.

A more detailed study of the metabolic effects of chloroquine in NIDDM revealed that the drug not only increased insulin secretion but that insulin clearance was reduced and peripheral glucose uptake accelerated [4]. Whether these three distinct effects operate in healthy travellers taking chloroquine prophylaxis or in patients with malaria during acute treatment is unknown but rare reports of serious chloroquine-associated hypoglycaemia in situations including overdose [5, 20, 30] implies that they are of limited biological significance. Despite concerns over toxicity, chloroquine can be given parenterally with safety in severe malaria [31]. However, chloroquine-resistant malaria is now widespread and the cinchona alkaloids and, more recently, artemisinin derivatives, are the drugs of choice in severely ill patients [1, 29]. Thus, one situation in which chloroquine metabolic effects might be important is now encountered rarely.

Mefloquine

In a recent placebo-controlled trial in young healthy Caucasian volunteers [6], 4 weeks of mefloquine in conventional prophylactic dose caused mild hyperinsulinaemia and a small (0.5 mmol l^{-1}) but statistically significant fall in plasma glucose. There were no such changes in the placebo group. Although subjects were not specifically requested to fast, most were in the post-absorptive state when blood was taken and sampling before and after mefloquine or placebo was done at the same time of day in each patient. The results of reanalysis of serum glucose and insulin concentrations using HOMA are shown in Figure 1. Mefloquine produced an average 60% increase in beta cell function at concentrations approaching those at steady state, a change equivalent to that after quinidine infusion in healthy Thai volunteers.

Mefloquine is related chemically to the cinchona alkaloids. These data, together with the finding that insulin secretion by rat islets of Langerhans is increased after exposure to mefloquine albeit at concentrations higher than in human plasma [32], suggest that it also has the ability to close beta cell K⁺-ATP channels. Furthermore, total plasma mefloquine concentrations appear close to the same log-linear dose-beta cell response relationship as quinine and quinidine (see Figure 2) though both prophylactic and treatment levels are usually less than those of the two cinchona alkaloids (<3 mg l^{-1}) [33]. However, mefloquine is at least 98% protein-bound [33] which means that enhanced beta cell function occurs at relatively low free drug concentrations (see Figure 3). The divergent effects of free serum quinine, quinidine and mefloquine on %B suggest that there are drug-specific differences in the nature of beta cell K⁺-ATP channel binding. Unfortunately, there are currently no in vivo data which allow an assessment of this. Principally because of poor solubility and irritant effects, mefloquine is not available as a parenteral preparation and so is not used in severe malaria. Analogous to the situation with chloroquine, this might have contributed to the apparently low rate of mefloquine-associated hypoglycaemia.

Other drugs

There have been no reported cases of hypoglycaemia associated with the use of halofantrine, a phenanthrone methanol related chemically to mefloquine. As in the case of mefloquine, the drug cannot be given parenterally and so its clinical use is restricted largely to treatment of uncomplicated cases. However, halofantrine administration is associated with clinically significant prolongation of the electrocardiographic QT interval [34], an effect which is also seen with quinine. If beta cell K⁺-ATP channel effects parallel those in myocardial K⁺ channels, it is possible that halofantrine also increases insulin secretion. This could contribute to or cause hypoglycaemia but, as with mefloquine, this may be an as yet unrecognized phenomenon. The combination of halofantrine and mefloquine appears particularly liable to promote serious dysrhythmias from QT effects [34] and, in clamp studies in diabetic patients, nild hypoglycaemia has itself been found to prolong the QT interval [35]. Cardiotoxicity with halofantrine, especially when used in combination and other drugs influencing ventricular repolarisation, could thus result from direct and indirect effects mediated through K⁺ channel activity at two sites.

The artemisinin derivatives have not been associated with hypoglycaemia and the proportions of patients with hypoglycaemia at study entry (8%) and during artesunate treatment (11%) in a recently-published series of adult patients with severe malaria [30] were similar. However, these compounds also prolong the QT interval in animals given high doses [36] and it is again possible that they also block pancreatic beta cell K⁺-ATP channels. However, these drugs and their active metabolites have relatively short half-lives [37, 38]. Any effect on insulin secretion may thus be short-lived and of limited clinical significance.

Treatment strategies

Although drug-induced inappropriate insulin secretion may be present, estimates of %S using CIGMA [25, 39] and of %S using the minimal model [26] have confirmed that malaria is associated with reduced insulin sensitivity. In combination
with adequate hepatic glucose production and normal counter-regulatory capacity, this may mean that euglycaemia is maintained despite hyperinsulinaemia. Hypoglycaemia will only occur when increased insulin secretion overrides these factors or the clinical situation changes such that glucose production decreases or utilisation increases significantly. Nevertheless, surveillance for, and aggressive treatment of, hypoglycaemia should be a central part of the routine management of acute falciparum malaria. Measurement of serum or plasma insulin may be available and will help to assess the contribution of antimalarial treatment to hypoglycaemia, but the nature of current assays mean that the result may not be available in time to influence clinical management.

In practical terms, intravenous dextrose replacement remains the mainstay of treatment for malaria-associated hypoglycaemia. Rapid injection of hypertonic dextrose (25 ml of a 50% w/v solution in adults or 1 ml kg⁻¹ body weight in children) is required where neuroglycopaenia is confirmed by blood or plasma glucose measurement, suspected where no such measurement is available, or considered imminent on the basis of serial blood glucose monitoring. Such treatment does not appear to be associated with subsequent adverse metabolic problems such as ‘rebound’ hypoglycaemia or hypokalaemia even when the patient has already received quinine [26, 40]. An adjustable-rate intravenous glucose infusion (e.g. 4 mg kg⁻¹ min⁻¹ in adults [41] or at least 6 mg kg⁻¹ min⁻¹ in children [42]) with frequent bedside blood glucose monitoring to maintain euglycaemia can be started either when hypoglycaemia is not severe or straight after a bolus injection of hypertonic dextrose. There are theoretical concerns that sustained hyperglycaemia may fuel tissue acidosis [43] and perhaps worsen neurological damage due to malaria and/or hypoglycaemia per se [44]. Thus, although strict euglycaemia should probably be the target, the method of glucose replacement may depend on the availability and standard of monitoring and treatment facilities.

Problems arise in patients in whom there are difficulties associated with intravenous administration of dextrose-containing fluids. In the case of renal impairment and potential fluid overload, hypoglycaemia can be corrected by instituting dialysis and increasing the glucose concentration of the dialysate. Hypertonic dextrose in dialysis fluid can, at the same time, help restore fluid balance. Where venous access is difficult and the patient is not vomiting, dextrose administration by nasogastric tube may be possible but its effect on blood glucose levels can be delayed and unpredictable.

Other measures can be instituted. Intramuscular or intravenous glucagon can, as in insulin over-treatment in diabetes, be given and repeated if necessary. The reduction of insulin secretion by somatostatin analogue given by the subcutaneous or intravenous route may be effective [45] but availability, expense and side-effects including suppression of the counter-regulatory response may limit its use. Measures to raise serum free fatty acid and triacyl glycerol concentrations and thus further decrease tissue insulin sensitivity through, for example, Intralipid™ with or without concomitant heparin administration, may also be effective in helping to raise plasma glucose concentrations in hypoglycaemia [40]. Again, local availability and other effects (such as increased bleeding with the use of heparin) may be problematic.

Patients are generally easier to manage once they are able to take glucose by mouth. If quinine is implicated in hypoglycaemia, it can be stopped and an alternative antimalarial regimen given. Although mefloquine or halofantrine might be considered in this situation because they constitute a less potent hyperglycaemic stimulus, these should be exercised as cardiotoxicity may result if plasma concentrations of quinine (which has a half-life of up to 24 h in acute malaria) are still significant as those of mefloquine or halofantrine are increasing. Artemisinin derivatives may be a particularly useful alternative.

When mefloquine and chloroquine are to be used as antimalarial prophylaxis, the traveller should probably be advised as to situations, such as heavy ethanol ingestion or prolonged fasting, in which the risks of hypoglycaemia are increased. This advice should also be given when mefloquine or quinine are prescribed as standby treatment, though quinine is used uncommonly in this situation. At present, there is insufficient information on halofantrine and artesinin derivatives to include or exclude these potentially useful standby medications when such advice is given.

Conclusions

Several established antimalarial drugs are known to promote insulin secretion which, in certain circumstances, may cause or contribute to hypoglycaemia. The common cellular mechanism of action is through closure of pancreatic beta cell K⁺ ATP channels. Quinine is the most potent of these drugs, though mefloquine appears to have significant effects on pancreatic beta cell function at very low plasma free concentrations. In the context of prophylaxis or standby treatment, travellers may need to be advised of situations in which drugs such as mefloquine may increase the risk of hypoglycaemia. In severe falciparum malaria, early recognition of hypoglycaemia is important, as is adequate treatment, since the consequences of neuroglycopaenia can be severe. There are no currently-available agents which can safely reverse the effects of drugs such as quinine on K⁺ ATP channels in patients with hyperinsulinaemic hypo-glycaemia. Intravenous glucose replacement remains the mainstay of treatment but adjunctive measures such as glucagon, somatostatin analogue and Intralipid™ infusion may have a place.

The help of Dr Jonathan Levy and other staff at the Diabetes Research Laboratories, Oxford University who provided the other measures can be instituted. Intramuscular or intravenous glucagon can, as in insulin over-treatment in diabetes, be given and repeated if necessary. The reduction of insulin secretion by somatostatin analogue given by the subcutaneous or intravenous route may be effective [45] but availability, expense and side-effects including suppression of the counter-regulatory response may limit its use. Measures to raise serum free fatty acid and triacyl glycerol concentrations and thus further decrease tissue insulin sensitivity through, for example, Intralipid™ with or without concomitant heparin administration, may also be effective in helping to raise plasma glucose concentrations in hypoglycaemia [40]. Again, local availability and other effects (such as increased bleeding with the use of heparin) may be problematic.

Patients are generally easier to manage once they are able to take glucose by mouth. If quinine is implicated in hypoglycaemia, it can be stopped and an alternative antimalarial regimen given. Although mefloquine or halofantrine might be considered in this situation because they constitute a less potent hyperglycaemic stimulus, these should be exercised as cardiotoxicity may result if plasma concentrations of quinine (which has a half-life of up to 24 h in acute malaria) are still significant as those of mefloquine or halofantrine are increasing. Artemisinin derivatives may be a particularly useful alternative.

When mefloquine and chloroquine are to be used as antimalarial prophylaxis, the traveller should probably be advised as to situations, such as heavy ethanol ingestion or prolonged fasting, in which the risks of hypoglycaemia are increased. This advice should also be given when mefloquine or quinine are prescribed as standby treatment, though quinine is used uncommonly in this situation. At present, there is insufficient information on halofantrine and artesinin derivatives to include or exclude these potentially useful standby medications when such advice is given.

Conclusions

Several established antimalarial drugs are known to promote insulin secretion which, in certain circumstances, may cause or contribute to hypoglycaemia. The common cellular mechanism of action is through closure of pancreatic beta cell K⁺ ATP channels. Quinine is the most potent of these drugs, though mefloquine appears to have significant effects on pancreatic beta cell function at very low plasma free concentrations. In the context of prophylaxis or standby treatment, travellers may need to be advised of situations in which drugs such as mefloquine may increase the risk of hypoglycaemia. In severe falciparum malaria, early recognition of hypoglycaemia is important, as is adequate treatment, since the consequences of neuroglycopaenia can be severe. There are no currently-available agents which can safely reverse the effects of drugs such as quinine on K⁺ ATP channels in patients with hyperinsulinaemic hypo-glycaemia. Intravenous glucose replacement remains the mainstay of treatment but adjunctive measures such as glucagon, somatostatin analogue and Intralipid™ infusion may have a place.

The help of Dr Jonathan Levy and other staff at the Diabetes Research Laboratories, Oxford University who provided the

References

3. Smith GD, Amos TA, Mahler R, Peters TJ. Effect of...


Antimalarial drugs and glucose metabolism


(Received 3 November 1996, accepted 27 January 1997)