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The pharmacokinetics and pharmacodynamics of quinine in the diabetic and non-diabetic elderly

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1 Quinine is a front-line antimalarial drug but is prescribed most commonly in non-malarious countries for cramps. Postural hypotension, hearing loss and hyperinsulinaemic hypoglycaemia occur in malaria and overdose but little is known of quinine kinetics and toxicity in the elderly.

2 We studied 12 non-insulin-dependent diabetics and 10 non-diabetic controls aged 51–79 years. Subjects attended on two occasions >7 days apart. On each test day, subjects were given a 600 Cal meal at 18.00 h (0 h) and, on one occasion, quinine sulphate 600 mg at 22.00 h (4 h). Venous blood samples for glucose, insulin and quinine assay were drawn pre-prandially and then regularly over the next 38 h. Supine and erect blood pressures were taken and audiometry was performed at 4, 6, 8 and 14 h. A one-compartment open pharmacokinetic model was fitted to serum quinine concentrations.

3 Absorption and elimination half-times, volume of distribution and oral clearance of quinine were comparable in the two groups ($P > 0.2$) and there was a mean absorption lag-time of approximately 1 h. Basal and immediate post-prandial (< 4 h) serum glucose and insulin concentrations on both test days were similar in the diabetics and also in the non-diabetics, but quinine produced a mean reduction in serum glucose of 1.0 mmol l^{-1} from 3–5 h post-dose in both groups without affecting serum insulin concentrations. Quinine administration did not alter postural blood pressure changes or produce significant hearing loss in either group.

4 These data suggest that a nocturnal post-prandial dose of quinine lowers early morning plasma glucose concentrations in both non-diabetic and diabetic subjects. Other potentially significant toxic effects in elderly patients were not observed.

Keywords quinine pharmacokinetics pharmacodynamics elderly non-insulin dependent diabetes mellitus

Introduction

Quinine has been used as an antimalarial agent for the last 200 years and remains the drug of choice for chloroquine-resistant falciparum malaria [1]. However, its most common use in non-malarious countries is as treatment for leg cramps. Reports vary regarding its efficacy in this setting [2–4] but significant numbers of elderly patients continue to take regular nocturnal doses of quinine as there are no other effective treatments available.

The pharmacokinetics of quinine have been studied extensively in patients with acute falciparum malaria [5–7] and also in young volunteers [8, 9]. Toxic effects, including 'cinchonism', cardiac conduction abnormalities, vascular instability with postural hypotension, high-frequency hearing loss, and hyperinsulinaemia with hypoglycaemia can occur in healthy fasting volunteers, patients with malaria and particularly overdose [7, 9–16]. However, compara-

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tively little is known about the disposition and toxicity of quinine when given in conventional doses to elderly subjects [4, 17]. It is possible that the widespread use of quinine in this group of patients may result in unrecognised but potentially deleterious effects, especially in the presence of concomitant illness and polypharmacy. Conversely, quinine may, through its stimulatory action on pancreatic beta cells [18], have a beneficial effect through improved glucose tolerance in patients with non-insulin-dependent diabetes mellitus (NIDDM).

The aim of the present study was to characterise the pharmacokinetic properties of quinine in elderly patients, both diabetic and non-diabetic, in circumstances in which the drug is usually taken (at night and postprandially), and to evaluate the effects of quinine on glucose tolerance, postural blood pressure changes and auditory acuity in these two patient groups.

Methods

Subjects

Twenty-two subjects were recruited (see Table 1). Twelve had NIDDM of mean (± s.d.) duration 3.9 ± 4.5 years. The 10 non-diabetics were matched as closely as possible with the diabetics for age, sex and body mass index (BMI). All the diabetics were recruited from outpatient clinics at Fremantle Hospital and had been taking gliclazide as sole hypoglycaemic medication at a fixed dose of between 40 and 320 mg daily for at least 2 weeks before study entry. The controls were all healthy non-blood relatives or friends of the diabetics. All subjects gave witnessed informed consent before recruitment. The study protocol was approved by the Fremantle Hospital Ethics Committee.

None of the diabetic patients had experienced symptomatic hypoglycaemia in the 2 weeks before study entry while 8 (67%) had a glycosylated haemoglobin level within the range associated with satisfactory glycaemic control (6–8%; see Table 1). Two diabetic and five non-diabetic hypertensives on β-adrenoceptor blockers or thiazide diuretics were the only subjects taking medications known to affect glucose tolerance other than gliclazide. In all seven cases, these drugs were stopped and strict monitoring of the blood pressure was instituted 48 h before each study day (see below). Five diabetics had mild peripheral sensory neuropathy but none had clinical evidence of autonomic neuropathy. A further six had other complications of diabetes including ischaemic heart disease, retinopathy and nephropathy (urinary albumin concentration > 30 mg l^{-1} on overnight specimen), but none of the 22 subjects had a serum creatinine > 130 μmol l^{-1} at study entry.

Table 1 Details of the 10 non-diabetic and 12 diabetic subjects at study entry. Age, body mass index and glycosylated haemoglobin are expressed as mean ± s.d.

	Non-diabetics	*Diabetics*
Age (years)	63.1 ± 6.5	62.7 ± 7.6
Sex (M/F)	5/5	7/5
Body mass index (kg m^{-2})	29.5 ± 6.8	29.2 ± 7.8
Glycosylated haemogobin (%)	<6.0	7.4 ± 1.4
Known hypertensives	2 (17%)	5 (42%)

Study design

Subjects were studied on two occasions at least 1 week apart. An identical protocol was followed each time except that subjects were randomised to receive quinine on only one test day ('quinine study' or QS *vs* 'no quinine study' or NQS). After admission to the Metabolic Ward, Fremantle Hospital at 17.00 h on the day of study, subjects were weighed, their height was measured, and they were placed on strict bed rest. At 17.30 h an intravenous cannula was inserted into a suitable forearm vein and kept patent by flushing with small volumes of sterile normal saline. Baseline blood samples for quinine, glucose and insulin assay were drawn into chilled tubes kept on wet ice at 18.00 h (time 0 h), and a bedside blood glucose estimation was determined to exclude hypoglycaemia.

A standard 600 Cal meal (75 g carbohydrate, 25 g fat and 20 g protein) was given immediately after the baseline sample and subjects were allowed only water for the next 10 h. Further venous samples for glucose and insulin alone were taken at 0.5, 1, 1.5, 2 and 4 h (22.00 h), at which time quinine sulphate (Rhône-Poulenc Rorer Australia Pty Ltd, Victoria, Australia) at a standard dose of 600 mg salt was administered to those allocated the drug. Sampling was continued at 4.5, 5, 5.5, 6, 7, 8, 9, 10 and 12, and at 14 h (08.00 h the following morning) when breakfast was given. In those who had received quinine, additional samples for serum quinine determination were taken at 18, 22, 28 and 38 h. Further bedside blood glucose estimations were performed at 4 h intervals during the study.

Supine and erect blood pressure measurements were taken during each study at 4, 6, 8 and 14 h (0, 2, 4 and 10 h post-quinine on the QS day). At each time-point, three supine readings were taken using a DinaMap Vital Signs Monitor 1846 SX (Critikon Incorporated, Florida, USA) followed by further measurements every 15 s for 5 min after standing. Audiometry was performed after each set of blood pressure recordings using a Maico MA40 audiometer (Maico Hearing Instruments, Minneapolis, USA) at frequencies of 0.5, 1.0, 2.0, 4.0, 6.0 and 8.0 mHz. Side-effects reported by the patients during the study were recorded on a standard form.

Assay methods

All blood samples were centrifuged and sera separated within 1 h of venepuncture. Serum glucose estimations were then performed immediately using the glucose oxidase method while sera for insulin and quinine determination were stored at −70° C and assayed subsequently. Samples for quinine assay were

taken and centrifuged under vacuum, and stored in small tubes filled to capacity so as to minimise changes in pH [19]. Serum insulin was measured by an immunoenzymometric method (Tosoh, Tokyo, Japan) and quinine by high performance liquid chromatography as described previously [20]. Inter- and intra-assay coefficients of variation for quinine were ≤ 5.0% at 1.0 mg l^{-1} and ≤ 4.8% at 5 mg l^{-1} with an assay detection limit of 0.1 mg l^{-1}. Free serum quinine concentrations were assayed after exclusion filtration through an Ultrafree-MC membrane (Millipore Corporation, Massachusetts, USA) using methods described previously [21].

Pharmacokinetic and statistical analysis

Pharmacokinetic analysis of serum quinine concentrations was performed using the iterative, least-squares curve-fitting programme PCNONLIN (Version 4; Statistical Consultants Incorporated, Kentucky, USA, 1992). A single-compartment open pharmacokinetic model was fitted to individual serum quinine profiles [6] and standard pharmacokinetic parameters, including an absorption lag time, were generated. Statistical analysis was by parametric statistics. Serum insulin concentrations were log-transformed prior to analysis. The trapezoidal rule was used to calculate areas under the glucose-time and insulin-time curves. Two-sample comparisons were by paired and unpaired *t*-tests, and analysis of variance (ANOVA) was used for multiple comparisons.

Results

Quinine pharmacokinetics and toxicity

On a body weight basis, the dose of quinine sulphate administered to the diabetic patients (mean (range) 6.3 (3.7–7.7) mg kg^{-1}) was similar to that given to the non-diabetic controls (5.8 (4.4–7.9) mg kg^{-1}; $P > 0.2$) on the QS day. Both total and free serum quinine concentrations in the two groups were comparable during the 34 h after oral quinine (Figure 1). There were no significant differences between the absorption and elimination half-times for quinine in the two groups and volumes of distribution (V/F) and oral clearance (CL/F) were also comparable ($P > 0.1$ in each case; Table 2). There was a mean absorption lag time of approximately 1 h in both groups. None of the patients experienced tinnitus, nausea, dysphoria or other symptoms of cinchonism after receiving quinine, although some reported dizziness during postural blood pressure testing. Simulation of steady-state serum quinine concentrations using mean values of pharmacokinetic parameters in each group and PCNONLIN suggested that typical peak serum concentrations would be of the order of 6 mg l^{-1} (free serum concentration 1 mg l^{-1}) on a once daily dose of 600 mg quinine sulphate taken post-prandially.

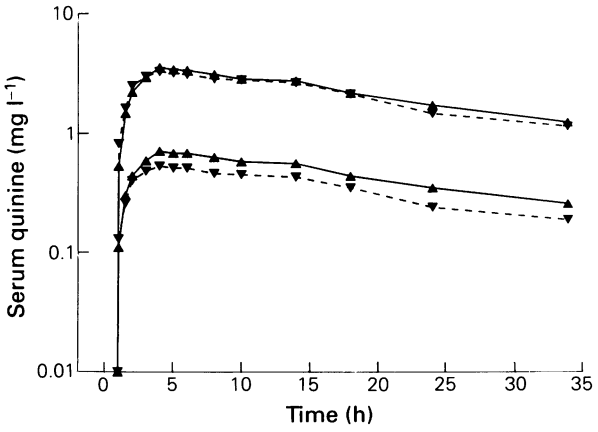

Figure 1 Mean total serum quinine concentrations in 10 non-diabetic (▼- - -▼) and 12 diabetic (▲——▲) subjects (upper lines) after 600 mg quinine sulphate by mouth. Corresponding mean serum free concentrations are also shown (lower two lines).

Table 2 Mean ± s.d. for quinine pharmacokinetic parameters in the 10 non-diabetic and 12 diabetic subjects derived from a one-compartment open model incorporating an absorption lag time. Median and (range) for percentage unbound drug are shown

	Non-diabetics	*Diabetics*	*95% CI on difference*
Volume of distribution (V/F) l kg^{-1}	1.70 ± 0.56	1.70 ± 0.63	0.56, −0.56
Absorption lag-time (t_{lag}) h	1.0 ± 0.5	1.2 ± 0.6	0.3, −0.7
Absorption half-time ($t_{½,abs}$) h	0.6 ± 0.2	0.7 ± 0.6	0.3, −0.5
Maximum concentration (C_{max}) mg l^{-1}	3.4 ± 0.8	3.7 ± 0.8	0.5, −1.1
Elimination half-time ($t_{½,z}$) h	19.9 ± 6.3	20.0 ± 7.5	6.4, −6.6
Systemic clearance (CL/F) ml kg^{-1} min^{-1}	1.07 ± 0.42	1.14 ±-0.58	0.41, −0.55
Serum unbound drug (%)	19 (10–39)	16 (9–24)	11, −3

Glucose homoeostasis

Serum glucose concentrations in the non-diabetic subjects are shown in Figure 2. Mean basal concentrations on both test days were comparable (4.9 ± 0.9 *vs* 5.3 ± 0.7 mmol l^{-1} for QS and NQS respectively; $P = 0.24$) and rose to peak post-prandial levels after an average of 1.5 h which were also similar (6.6 ± 1.1 *vs* 6.5 ± 0.5 mmol l^{-1}; $P = 0.72$). At 4 h (immediately before quinine was given on the QS day), mean serum glucose values remained comparable (5.6 ± 0.6 *vs* 5.6 ± 0.5 mmol l^{-1}; $P = 0.94$). These individual concentration data paralleled the areas under the glucose-time curve for the first 4 h of the study (AUC(0,4); 23.6 ± 2.8 *vs* 22.7 ± 2.1 mmol l^{-1} h for QS and NQS respectively; $P = 0.25$).

After quinine administration (4 h) in the non-diabetic group, there was a consistent fall in serum glucose of 1.2 ± 0.4 mmol l^{-1} over the next 4 h. Serum glucose levels at the same time in the NQS (between 4 and 8 h) remained relatively stable (mean fall 0.4 ± 0.4 mmol l^{-1}; $P = 0.0001$ *vs* QS). Consistent with this observation, the AUC(4,14) values were also significantly different on the two test days, being consistently lower after quinine (49.8 ± 4.9 *vs* 55.4 ± 5.6 mmol l^{-1} h for QS and NQS respectively; $P = 0.0005$).

Serum insulin profiles for the non-diabetic group are shown in Figure 2. The basal (geometric mean (−1 s.d. to +1 s.d.); 17 (6–49) *vs* 15 (7–31) mu l^{-1}) and integrated post-prandial insulin concentrations (AUC(0,4); 129 (71–236) *vs* 125 (75–208) mu l^{-1} h) were similar on the QS and NQS days, respectively ($P > 0.6$). Changes in serum insulin after 4 h (the time of quinine administration on the QS day) were also comparable (AUC(4,14); 130 (80–212) *vs* 129 (72–232) mu l^{-1} h for QS and NQS, respectively; $P = 0.9$) in the presence of significantly different serum glucose responses.

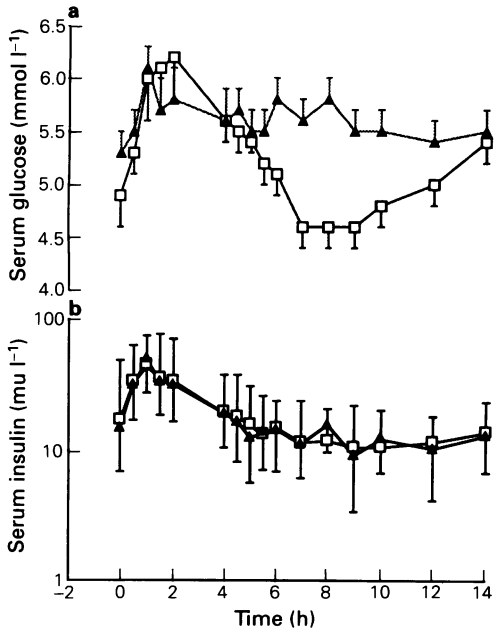

Figure 2 Mean ± s.d. serum glucose concentrations (a) and logarithmic mean ± s.d. serum insulin concentrations (b) in 10 non-diabetic subjects following a standard meal at 0 h, with (□——□) or without (▲——▲) 600 mg quinine sulphate by mouth at 4 h.

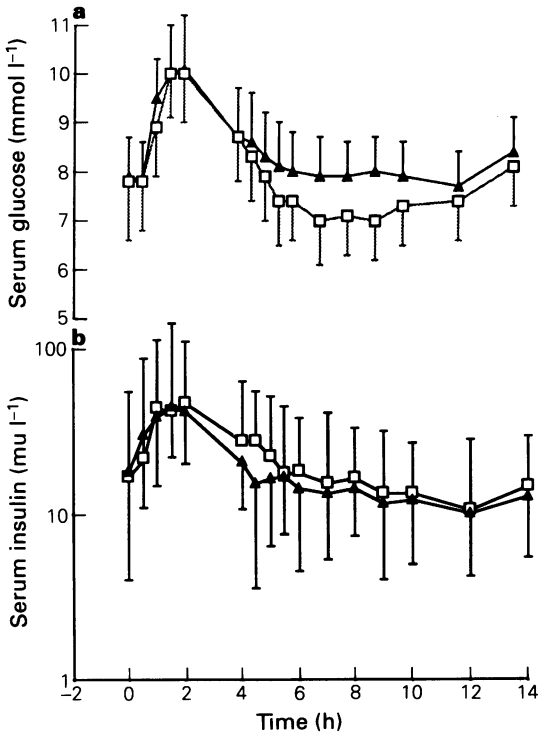

Figure 3 Mean ± s.d. serum glucose concentrations (a) and logarithmic mean ± s.d. serum insulin concentrations (b) in 12 diabetic subjects following a standard meal at 0 h, with (□——□) or without (▲——▲) 600 mg quinine sulphate by mouth at 4 h.

The diabetic patients showed much greater between-subject variability in serum glucose and insulin responses than the non-diabetics. Serum glucose concentrations during the QS and NQS in the 12 diabetics were similar at baseline (7.8 ± 4.0 *vs* 7.9 ± 2.9 mmol l^{-1}), at their peak an average of 2 h post-prandially (10.6 ± 3.2 *vs* 10.6 ± 3.2 mmol l^{-1}) and at 4 h (8.7 ± 3.0 *vs* 8.7 ± 3.4 mmol l^{-1}, respectively; $P > 0.8$ in each case; Figure 3). These data reflected AUC(0,4) values (36.5 ± 12.4 and 36.8 ± 12.9 mmol l^{-1} h for QS and NQS, respectively; $P = 0.25$) which were, on average, 50% greater than those of the non-diabetic subjects.

On the NQS day, the serum glucose continued to fall after 4 h (Figure 3) but had risen again to levels above baseline at 14 h (08.00 h the next morning). After oral quinine was given during the QS (at 4 h), there was also a consistent fall in serum glucose to mean levels at 7–10 h (3–5 h after quinine) which were approximately 1.0 mmol l^{-1} lower than those during the same period in the NQS (Figure 3). Despite the fact that serum glucose concentrations at 9 h (around the time the serum quinine concentration was maximal during the QS) were significantly lower after quinine (7.0 ± 2.8 *vs* 8.0 ± 2.4 mmol l^{-1}; $P < 0.02$), the difference between the mean AUC(4,14) values on the two study days did not achieve statistical significance (74.5 ± 28.1 *vs* 79.9 ± 25.6 mmol l^{-1} h for QS and NQS, respectively; $P = 0.24$).

The serum insulin profiles in the diabetic group were temporally and quantitatively similar to those observed in the non-diabetics (Figures 2 and 3). In the 12 diabetic subjects, serum insulin responses during the first 4 h were similar on the two study days (basal concentrations 17 (5–54) *vs* 18 (4–78) mu l^{-1} and AUC(0,4) values 148 (60–367) *vs* 139 (66–291) mu l^{-1} h for QS and NQS, respectively; $P > 0.6$; see Figure 3). However, there was a tendency for AUC(4,14) values to be greater after quinine than on the NQS day (157 (74–333) *vs* 134 (61–292) mu l^{-1} h, respectively; $P = 0.06$).

Assessment of individual patient data revealed that, even on the QS day, all serum glucose concentrations remained > 3.0 mmol l^{-1}. Amongst the non-diabetic subjects, the greatest fall in serum glucose on the QS day was 1.9 mmol l^{-1}. In the diabetic group, the greatest decrease in serum glucose concentration was 5.5 mmol l^{-1} (from 13.0 mmol l^{-1} to 7.5 mmol l^{-1}) in the 8 h after quinine was given. There were no significant correlations between peak serum quinine concentration and the fall in serum glucose after quinine administration in either group ($r = -0.26$ in each case; $P > 0.2$) but, due to the study design, the values of both variables were distributed over narrow ranges.

Postural blood pressure changes

Both the supine systolic blood pressure (SBP) and maximum fall in SBP during the 5 min after standing in each of the two groups and at each time-point are summarised in Table 3. There were no significant differences at baseline (4 h) in either supine SBP or maximum SBP fall between the two study days by group (ANOVA; $P > 0.05$, respectively). This was also the case at 6, 8 and 14 h (08.00 h the following morning). However, the non-diabetic subjects tended to have the greater baseline postural fall in SBP, and there was a trend to an increasingly greater fall in SBP at the later study times regardless of group and study day (see Table 3). The changes in diastolic blood pressure were quantitatively smaller but showed the same trend (data not shown).

Table 3 Mean ± s.d. maximum fall in systolic blood pressure after standing on the test days when quinine was (QS) and was not (NQS) given. Data [in parentheses] are mean ± s.d. systolic blood pressures at 22.00 h (4 h)

	Non-diabetics		*Diabetics*	
Time	*NQS*	*QS*	*NQS*	*QS*
22.00 h (4 h)	20 ± 8 [133 ± 13]	27 ± 17 [140 ± 22]	14 ± 12 [130 ± 18]	15 ± 15 [123 ± 10]
24.00 h (6 h)	27 ± 13	28 ± 17	16 ± 13	17 ± 16
02.00 h (8 h)	28 ± 10	33 ± 21	22 ± 11	20 ± 13
08.00 h (10 h)	39 ± 11	32 ± 14	26 ± 16	24 ± 14

Table 4 Median [absolute range] hearing loss relative to that at baseline (20.00 h or 4 h) assessed from right ear on the test days when quinine was (QS) and was not (NQS) given

	Non-diabetics		*Diabetics*	
Time	*QS*	*NQS*	*QS*	*NQS*
i) 500 Hz				
24.00 h (6 h)	−5 [−15–10]	0 [−20–15]	0 [−10–10]	0 [−15–30]
02.00 h (8 h)	0 [−15–15]	−5 [−30–20]	0 [−15–10]	0 [−25–15]
08.00 h (10 h)	0 [−20–10]	−2.5 [−35–45]	0 [−10–10]	2.5 [−25–10]
ii) 6000 Hz				
24.00 h (6 h)	0 [−10–10]	5 [−15–15]	5 [−10–15]	2.5 [−15–45]
02.00 h (8 h)	2.5 [−15–20]	2.5 [−10–15]	5 [−10–20]	0 [−20–20]
08.00 h (10 h)	10 [−10–20]	2.5 [−15–15]	10 [−15–35]	2.5 [−15–35]

Auditory acuity

Representative data from acuity testing at 500 and 6000 Hz are summarised in Table 4. There were no significant differences in hearing loss at 4 h (baseline) between the two study days by patient group for each frequency used (ANOVA; $P > 0.05$ in each case) though there was wide inter-individual variation in hearing loss. As a result, changes in auditory acuity from the 4 h baseline were compared, with no significant differences between subject groups, test day and time in evidence ($P > 0.05$ in each case).

Discussion

The side-effects of drugs prescribed mainly for the elderly are not always easy to recognise. As is the case with quinine-induced dizziness and hearing loss, they may be common problems in other clinical contexts and difficult to relate to medications which are not taken regularly or at exactly the same time of day. Moreover, in the case of drugs such as quinine which are usually prescribed at night, the patient may only be aware of toxicity when awake or out of bed during the early morning hours. By contrast, quinine-induced hyperinsulinaemia would theoretically benefit elderly patients with NIDDM and nocturnal hyperglycaemia, but might also be deleterious in those with low-normal or depressed plasma glucose concentrations at a time when unawareness of hypoglycaemia is at its greatest. The present study was designed to assess these concerns.

Doses of quinine ranging from a single 300 mg tablet of the bisulphate salt (equivalent to 178 mg quinine base) to 600 mg (two tablets) of quinine sulphate (representing 496 mg base) are prescribed commonly for cramps. Bioavailability of the sulphate

salt is of the order of 80–90% [22]. In the present study, 600 mg quinine sulphate was given post-prandially to previously untreated subjects in an attempt to reproduce a common clinical situation in which the pharmacokinetic and pharmacodynamic properties of quinine could best be studied. Subjects tolerated the dose well with no complaints of side-effects over a period of observation which was well beyond the half-life of the drug in all cases.

In both groups of subjects, there was a significant lag time of between 0.5 and 2.7 h after oral administration before serum quinine concentrations began to rise. Previous studies of quinine disposition in the elderly have either not addressed this effect [4] or administered the drug to fasting subjects [17]. Fasting is known to accelerate gastric emptying while fat-containing solid foods and a supine rather than an erect posture are factors which would have contributed to delayed gastric emptying in our series [23]. Although there was no significant difference between absorption lag times and half-times in our diabetic and non-diabetic groups, it is likely that diabetics with gastroparesis due to autonomic neuropathy would have even greater delays in quinine absorption.

The serum quinine concentration profiles and derived pharmacokinetic parameters were similar in the two patient groups and, allowing for differences in dosage, formulation and subject body weights, to those found previously in other healthy elderly subjects [4, 17]. Serum free drug concentrations in our series, determined under standardised conditions, were generally higher than those reported by some authors [17, 21, 24] but not others [25, 26]. These discrepancies may be due, in part, to differences in sample pH and a_1-acid glycoprotein concentrations [19]. Nevertheless, there was no significant difference between quinine plasma protein binding in our two subject groups. This is consistent with the fact that interactions between gliclazide and quinine, including protein binding displacement, have not been reported previously [27]. In all subjects, predicted peak total serum quinine concentrations at steady-state were well below the range at which significant toxicity is usually observed (> 10 mg l^{-1}; [28]), though elderly patients with a low body weight and/or renal impairment might be at risk of increased serum concentrations and side-effects on a daily 600 mg quinine sulphate regimen.

As judged from serum concentration profiles on the study days when quinine was not administered, our diabetic patients had both pre- and post-prandial hyperglycaemia in the presence of serum insulin concentrations which were comparable with those in closely-matched non-diabetic controls studied under identical conditions. The simplest interpretation of this observation is that insulin resistance was present in the diabetic subjects, independent of the effects of confounding variables such as obesity [29]. From 3–6 h after quinine was given, serum glucose concentrations fell by an average of 1 mmol l^{-1} in both subject groups relative to values obtained at the same times on the day when quinine was not administered, while serum insulin profiles were essentially unchanged. This suggests that quinine was responsible for significant changes in insulin sensitivity and/or pancreatic beta-cell function in both diabetic and non-diabetic subjects.

There is some evidence from animal studies that insulin sensitivity is increased by chronic quinine administration [30], an effect which could be mediated through enhanced transmembrane glucose transport [31]. Other authors have suggested that increased glucose disposal is due to increased plasma insulin *per se* [32]. Quinine reliably stimulates beta cell insulin secretion *in vitro* [18] and in young, healthy volunteers, especially when plasma glucose concentrations are above the normal fasting range [10, 11, 16]. The fact that serum insulin levels were not increased by quinine in the diabetic group despite hyperglycaemia suggests that these patients, as might be expected [29], had significant pancreatic beta-cell dysfunction as well as insulin resistance. Nevertheless, given the similar glucose and insulin profiles in both groups of subjects, it is tempting to postulate that quinine increases tissue glucose utilisation post-prandially while maintaining insulin secretion in the presence of falling plasma glucose concentrations.

Quinine has a peripheral vasodilator action and has been associated with marked postural hypotension in patients being treated for acute falciparum malaria [15, 33]. It has been postulated that this effect is mediated through the inhibition of the actions of aldosterone and angiotensin [34]. In both our patient groups, there was an average maximum fall in systolic blood pressure up to 5 min after standing of approximately 15–25 mm Hg at baseline which had increased progressively to 25–40 mm Hg by 08.00 h the following morning irrespective of whether quinine had been administered or not. In young patients convalescing from falciparum malaria, quinine given in the same dose as the present study did not affect postural blood pressure changes [15]. However, during acute illness in the same subjects, quinine significantly worsened pre-treatment postural hypotension on a background of abnormal cardiovascular counterregulatory reflexes. Such autonomic dysfunction is a well-recognised neurological complication of diabetes [35]. Consistent with data from healthy young volunteers receiving intravenous quinine [9], auditory acuity tended to be lower at high frequencies the morning after quinine administration but this did not reach statistical significance.

The present data suggest that the absorption of a conventional dose of quinine given after a meal is significantly delayed in healthy elderly subjects and those with NIDDM. An average reduction of approximately 1 mmol l^{-1} in early morning plasma glucose concentrations can be expected after nocturnal quinine administration in both patient groups. This may improve overall glycaemic control in NIDDM patients but may also predispose to early morning, perhaps unrecognised hypoglycaemia in patients with previously good blood glucose control. Significant cardiovascular and auditory toxicity was not observed and would seem, on the basis of predicted steady-

state serum concentration profiles, unlikely sequelae in elderly patients receiving conventional daily doses of quinine.

Diabetic patients with autonomic neuropathy may, however, be at risk of the toxic effects of quinine. Such patients can have depressed counterregulatory responses to quinine-induced hypoglycaemia and may be more susceptible to the effects of the drug on postural blood pressure changes. Further studies in this and other sub-groups of NIDDM patients (such as those with nephropathy) would be valuable, especially as the incidence of NIDDM is increasing in Western countries and quinine continues to be used frequently as empirical treatment for nocturnal cramps.

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References

1 Warrell DA, Molyneux ME, Beales PF (eds). Severe and complicated malaria. *Trans Roy Soc trop Med Hyg* 1990; **84** (suppl.): 1–65.

2 Connolly PS, Shirley EA, Wasson JH, Nierenberg DW. Treatment of nocturnal leg cramps. A crossover trial of quinine *vs* vitamin E. *Arch intern Med* 1992; **152**: 1877–1880.

3 McGee SR. Muscle cramps. *Arch intern Med* 1990; **150**: 511–518.

4 Warburton A, Royston JP, O'Neill CJA, *et al.* A quinine a day keeps the leg cramps away? *Br J clin Pharmac* 1987; **23**: 459–465.

5 Davis TME, White NJ, Looareesuwan S, Silamut K, Warrell DA. Quinine pharmacokinetics in cerebral malaria: predicted plasma concentrations after rapid intravenous loading using a two-compartmental model. *Trans Roy Soc trop Med Hyg* 1988; **82**: 542–547.

6 Supanaranond W, Davis TME, Pukrittayakamee S, *et al.* Disposition of oral quinine in acute falciparum malaria. *Eur J clin Pharmac* 1991; **40**: 49–52.

7 White NJ, Looareesuwan S, Warrell DA, Warrell MJ, Bunnag D, Harinasuta T. Quinine pharmacokinetics and toxicity in cerebral and uncomplicated falciparum malaria. *Am J Med* 1982; **73**: 564–572.

8 White NJ, Chanthavanich P, Krishna S, Bunch C, Silamut K. Quinine disposition kinetics. *Br J clin Pharmac* 1983; **16**: 399–403.

9 Karbwang J, Davis TME, Looareesuwan S, Molunto P, Bunnag D, White NJ. A comparison of the pharmacokinetic and pharmacodynamic properties of quinine and quinidine in healthy Thai males. *Br J clin Pharmac* 1993; **35**: 265–271.

10 Davis TME, Pukrittayakamee S, Supanaranond W, *et al.* Glucose metabolism in quinine-treated patients with uncomplicated falciparum malaria. *Clin Endocrinol (Oxf)* 1990; **33**: 739–749.

11 Davis TME, Karbwang J, Looareesuwan S, Turner RC, White NJ. Comparative effects of quinine and quinidine on glucose metabolism in healthy volunteers. *Br J clin Pharmac* 1990; **30**: 397–403.

12 Jaeger A, Sauder P, Kopferschmitt J, Flesch F. Clinical features and management of poisoning due to antimalarial drugs. *Med Toxicol* 1987; **2**: 242–273.

13 Okitolonda W, Delacollette C, Malengreau M, Henquin JC. High incidence of hypoglycaemia in African patients treated with intravenous quinine for severe malaria. *Br med J* 1987; **195**: 716–718.

14 Roche RJ, Silamut K, Pukrittayakamee S, *et al.* Quinine induces reversible high-tone hearing loss. *Br J clin Pharmac* 1990; **29**: 780–782.

15 Supanaranond W, Davis TME, Pukrittayakamee S, Nagachinta B, White NJ. Abnormal circulatory control in falciparum malaria. *Eur J clin Pharmac* 1993; **44**: 325–329.

16 White NJ, Warell DA, Chanthavanich P, *et al.* Severe hypoglycemia and hyperinsulinemia in falciparum malaria. *New Engl J Med* 1983; **309**: 61–66.

17 Wanwimolruk S, Chalcroft S, Coville PF, Campbell AJ. Pharmacokinetics of quinine in young and elderly subjects. *Trans Roy Soc trop Med Hyg* 1991; **85**: 714–717.

18 Henquin J-C, Horemans B, Nenquin M, Verniers J, Lambert AE. Quinine-induced modifications of insulin release and glucose metabolism by isolated pancreatic islet cells. *FEBS Lett* 1975; **57**: 280–284.

19 Winstanley P, Newton C, Watkins W, *et al.* Towards optimal regimens of parenteral quinine for young African childen with cerebral malaria: the importance of unbound quinine concentration. *Trans Roy Soc trop Med Hyg* 1993; **87**: 201–206.

20 Rauch K, Ray J. Improved high-performance liquid chromatographic method for the determination of quinine in plasma. *J Chromatogr* 1988; **430**: 170–174.

21 Silamut K, White NJ, Looareesuwan S, Warrell DA. Binding of quinine to plasma proteins in falciparum malaria. *Am J trop Med Hyg* 1985; **34**: 681–686.

22 Hall AP, Czerwinski AW, Madonia EC, Evensen KL. Human plasma and urine quinine levels following tablets, capsules and intravenous infusion. *Clin Pharmac Ther* 1973; **14**: 580–585.

23 Gibaldi M. *Biopharmaceutics and clinical pharmacokinetics*. Philadelphia, Lea and Febiger 1984: 38–40.

24 Mihaly GW, Ching MS, Kleijn MB, Paull J, Smallwood RA. Differences in binding of quinine and quinidine to plasma proteins. *Br J clin Pharmac* 1987; **24**: 769–774.

25 Berlin CM, Stackman JM, Vessell ES. Quinine-induced alterations in drug disposition. *Clin Pharmac Ther* 1975; **18**: 670–679.

26 Mansor SM, Molyneux ME, Taylor TE, Ward SA, Wirima JJ, Edwards G. Effect of *Plasmodium falciparum* malaria infection on the plasma concentration of α_1-acid glycoprotein and the binding of quinine in Malawian children. *Br J clin Pharmac* 1991; **32**: 317–321.

27 Krall LP. *Gliclazide in perspective*. Chester, Adis International Limited 1991; 8–15.

28 Powell RD, McNamara JV. Quinine: side-effects and plasma levels. *Proc helminth Soc Wash* 1972; **39**: 331–338.

29 Reaven GM. Insulin secretion and insulin action in non-insulin-dependent diabetes mellitus: which defect is primary? *Diabetes Care* 1984; **7** (suppl.): 17–24.

30 Oku J, Bray GA, Fisler JS. Effects of oral and parenteral quinine on rats with ventromedial knife-cut obesity. *Metabolism* 1984; **33**: 538–544.
31 James DR, Stansbie D. Familial pseudohyperkalaemia: inhibition of erythrocyte K^+ efflux at 4° C by quinine. *Clin Sci* 1987; **73**: 557–560.
32 Okitolonda W, Pottier A-M, Henquin J-C. Glucose homoeostasis in rats treated acutely and chronically with quinine. *Eur J Pharmac* 1986; **132**: 179–185.
33 Kofi-Ekue JM, Phiri DED, Mukunyandela M, *et al.* Severe orthostatic hypotension during treatment of falciparum malaria. *Br med J* 1987; **296**: 396.
34 Hadjokas N, Goodfriend T. Inhibition of aldosterone production and angiotensin action by drugs affecting potassium channels. *Pharmacology* 1991; **43**: 141–150.
35 Stevens MJ, Edmonds ME, Mathias CJ, Watkins PJ. Disabling postural hypotension complicating diabetic autonomic neuropathy. *Diabetic Med* 1991; **8**: 870–874.

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