GASTROINTESTINAL FUNCTION, QUININE ABSORPTION AND PARASITE RESPONSE IN FALCIPARUM MALARIA

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INTRODUCTION

Persons ill with acute falciparium malaria often have gastrointestinal symptoms, the most common of which are anorexia, nausea and vomiting. (Glor, 1969). Gastrointestinal function has been shown to be abnormal in patients with acute falciparum malaria. Olsson and Johnston (1969) found impaired d-xylose absorption and documented histopathologic changes in intestinal biopsy specimens taken from American soldiers infected with malaria. These observations were confirmed and extended by Karney and Tong (1972) using additional indicators of absorptive function. In neither of these studies were serum concentrations of orally administered antimalarial drugs and/or parasite response correlated with absorptive function.

Intestinal abnormalities in asymptomatic persons indigenous to tropical areas are reported to be widespread (Klipstein, 1968). Results of studies of the prevalence of histopathologic changes (Sprinz *et al.*, 1962) and functional abnormalities in Thai subjects gave results similar to those obtained elsewhere (Troncale *et al.*, 1967). The relevance of these findings to nutrition and health is unclear. Since malaria is endemic in areas of Thailand where malabsorption might be prevalent, it is important to understand what implication, if any, malabsorption has for oral antimalarial chemotherapy.

Plasmodium falciparum-infected and uninfected subjects were studied to determine whether previous work demonstrating mild reduction of absorptive function could be documented, whether falciparum infection was associated with a further decrement in that function, whether malabsorption produced slow responses to the orally administered antimalarial, and whether absorptive function improved rapidly with successful antimalarial therapy.

MATERIALS AND METHODS

Patients: The study was carried out between January and June 1973 at the Trad Provincial Hospital in southeast Thailand. Two groups of adult males were included, a falciparum malaria-infected study group and an uninfected "control" group. The falciparum-infected group consisted of 29 patients assigned to the quinine treatment group of an investigational new drug protocol. (Hall *et al.*, 1974).

Only patients with clinically mild or moderate disease were studied. Patients who were seriously ill (e.g. with high parasitaemia, hypotension, or jaundice) were excluded. These patients were treated with 540 mg (base) of quinine-sulfate (in sugar-coated tablets) every 8 hours for 18 doses (total dose 9.72 gms). D-xylose absorption studies (using a 5-gram dose) were performed on the first and sixth days of hospitalization.

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A blood specimen was collected for the serum d-xylose determination two hours after dosing. Urine d-xylose was determined from a pooled 5-hour collection begun at the time of dosing. Specimens for serum quinine determination were obtained two hours after quinine administration on the same days. Specimens for serum carotene, bilirubin, glutamic oxaloacetic transaminase, alkaline phosphatase, and creatinine were collected on the first and sixth days of hospitalization and again on the twenty-eighth day.

The control group consisted of 10 non-malaria patients who had no evidence of gastrointestinal or renal disease and eight healthy laboratory workers. The former were selected as the next admission, willing to participate, following the admission of a falciparum-infected patient. Eight of the ten control patients were admitted with a history of febrile illnesses, but had at least two negative thick-thin malaria smears in the course of their workup. A (5-gram) d-xylose test was performed once, on the first full day of hospitalization. A single specimen for serum carotene, bilirubin, glutamic oxaloacetic transaminase, alkaline phosphatase, and creatinine was also obtained. Since the results from control patients and laboratory workers did not differ, data from both groups are combined hereafter.

A stool specimen was collected from each study subject during hospitalization and examined for ova and parasites. Quantitative determinations for malaria parasites were performed by the method of Earle and Perez (1932). Serum and urinary d-xylose levels were determined by the method of Meites and Faulkner (1962). Serum quinine, was assayed by the method of Cramer and Isaksson (1963). Serum creatinine, bilirubin, glutamic oxalacetic transaminase, and alkaline phosphatase determinations were performed by standard laboratory methods. Intestinal biopsies were not performed.

RESULTS

The d-xylose dose was administered without difficulty in all subjects except one. In this falciparum-infected patient, the dose was vomited and a second dose was given the following morning. Five hour urine volumes were above 150 ml. in all subjects tested except for one control. The laboratory data are shown in Table 1. Of the 29 malaria-infected patients, 17% had decreased serum d-xylose, 55% decreased urinary d-xylose excretion, and 37% decreased serum carotene on day one. Of the 18 control subjects, in comparison, 13% had low serum d-xylose, 29% low urinary d-xylose excretion, and 31 % low serum carotene.

Table 1

Results of serum and urine d-xylose and serum carotene determinations in falciparum-infected and uninfected (control subject).

	Falciparum-infected subjects			Uninfected (control) subjects		
	Serum d-xylose (mg %)	Urine d-xylose (gm/5 hrs)	Serum carotene (μg %)	Serum d-xylose (mg %)	Urine d-xylose (gm/5 hrs)	Serum carotene (μg %)
Day 1	6.59 ± 3.66*	1.11 ± 0.49	58.7 ± 25.9	8.42 ± 3.66	1.49 ± 0.49	71.2 ± 36.8
Day 6	7.65 ± 4.25	1.06 ± 0.52	62.8 ± 28.1	N.D.**	N.D.	N.D.

Normal values: serum d-xylose >4.2 mg%; urine d-xylose >1.2 gm/5 hrs; serum carotene = >50 μg%.
*Mean ± S.D.
**Not done

Day one mean values for each of these variables were less in the falciparum-infected patients, but not significantly so. In addition mean values for serum d-xylose and serum carotene increased and that for urinary d-xylose excretion decreased between the first and second examinations in the malaria-infected patients. Again none of these changes was statistically significant.

The parasite counts on admission ranged from 1,820 to 76,431 asexual parasites per c.mm in the falciparum-infected patients. These initial levels of parasitaemias did no correlate well with day one d-xylose determinations (Fig. 1). All 29 patients completed the course of quinine therapy and were cured except for one case which recrudesced 15 days after treatment. The mean serum quinine concentration on the first full day of treatment was 11.04 mg/L and on the sixth day 8.55 mg/L. This difference is statistically significant ($p < 0.01$). There was poor correlation between initial serum d-xylose and initial serum quinine concentrations (Fig. 2). Neither this correlation nor the one above (Fig. 1) were improved by substituting

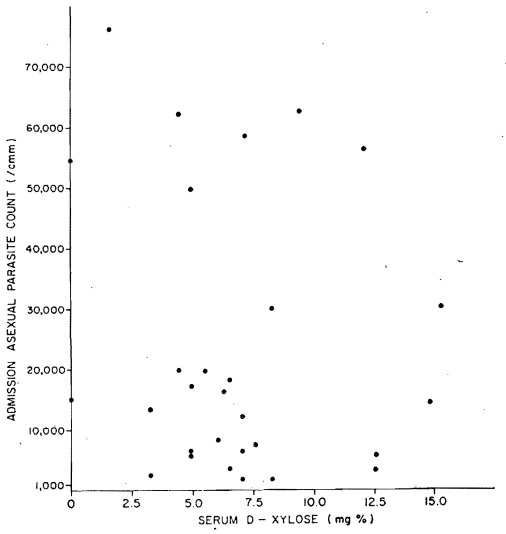

Fig. 1—Scatter diagram of admission parasite counts versus day 1 serum d-xylose levels in 29 patients, r = 0.14.

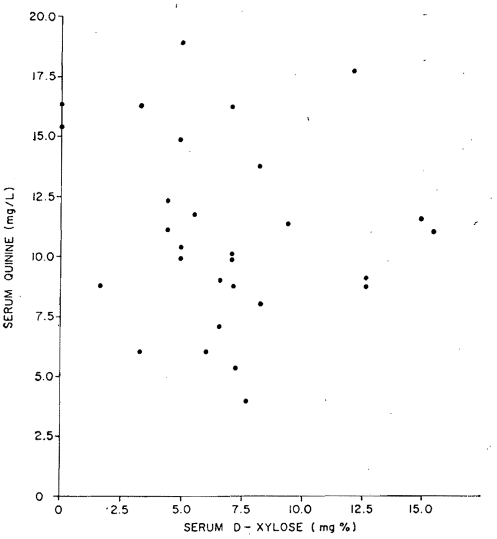

Fig. 2—Scatter diagram of day 1 serum quinine levels versus day 1 serum d-xylose levels in 29 patients, r = 0.16.

urinary d-xylose for serum d-xylose values ($r = -0.0375$ and $r = -0.1970$ respectively). Further, initial serum quinine concentrations did not correlate well with parasite clearance time (Fig. 3), even when the clearance times

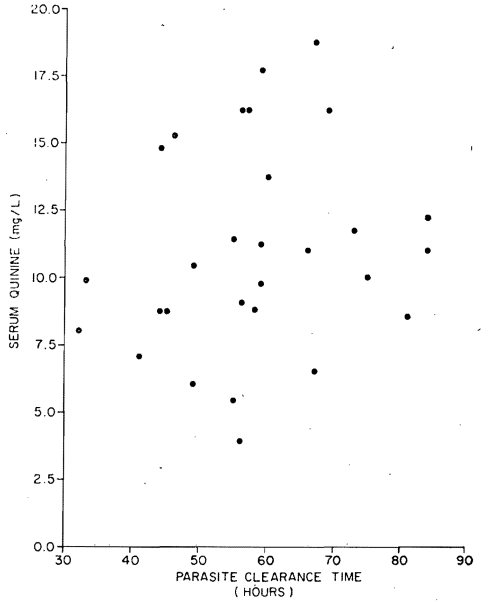

Fig. 3—Scatter diagram of day 1 serum quinine levels versus parasite clearance times in 29 patients, r = 0.19.

were corrected for the degree of initial parasitemia.

Twelve of the malaria-infected patients (41%) and 8 of the controls (44%) were infected with one or more intestinal helminths, hookworm being the most common (18/20). Serum d-xylose and carotene concentrations and urinary d-xylose excretion did not differ in subjects with or without intestinal parasitism. Two malaria-infected patients had elevated serum bilirubin, 5 control subjects had elevated serum transaminase values. No person in either group had elevated serum creatinine.

DISCUSSION

The results of measurements of intestinal absorptive function reported here were comparable to those obtained during an earlier study conducted in Thai subjects (Troncale *et al.*, 1967). Our study did not address itself primarily to the question of whether or not these measurements indicate the range of normal values for this population or identify those with subclinical intestinal disease. We did find that although intestinal absorptive function, as measured by serum and urinary d-xylose and serum carotene studies, was less in malaria-infected than uninfected Thai subjects, the differences were slight and not statistically significant. The data thus suggest a distinction between this population and United States military populations, in whom malarial infection clearly caused a decrease in absorptive function. (Olsson and Johnston, 1969; Karney and Tong, 1972).

If absorptive function was further decreased in the malaria-infected subjects, yet not discernible by our measurements, that function was not correlated with the degree of the initial parasitaemia nor was it improved acutely by effective antimalarial chemotherapy. The almost complete absorption of orally administered quinine, even in subjects with severe diarrhoea (Rollo, 1970), probably explains the lack of correlation between serum quinine concentrations and d-xylose results. The serum quinine concentrations attained in these (presumably partially-immune) patients produced rapid parasite clearance in all and radical cure in all but one. The results of the present study thus suggest that malabsorption, if present, is of little clinical significance in patients who have mild or moderate disease. Since inpatients with parasitaemias greater than 100,000 asexual forms per milliliter or those severely ill should receive intravenous quinine dihydrochloride, the question of malabsorption is academic.

Our observations that serum quinine concentrations attained are greater early in therapy than later confirm the findings of others. (Brooks *et al.*, 1969; Powell and McNamara, 1972). It has been suggested that changes in quinine concentrations during therapy may be related not to altered urinary excretion but rather to altered drug metabolism occurring while the patient is febrile. (Trenholme pers. comm.)

SUMMARY

A controlled study was performed in falciparum malaria-infected Thai patients to assess the occurrence and clinical significance of malabsorption and quinine bioavailability. Urinary excretion of d-xylose and serum d-xylose and carotene concentrations were slightly less in infected subjects. There was poor correlation between the degree of initial parasitaemia and d-xylose serum concentration and urinary excretion, between d-xylose results and serum quinine concentrations, and between quinine results and parasite clearance times. These data suggest that if falciparum malaria causes a

decrement in absorptive function in this population, it is minimal and of little clinical significance.

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