DRUG INTERACTION BETWEEN CYCLOSPORINE A AND QUININE IN A RENAL TRANSPLANT PATIENT WITH MALARIA

H W Tan, S L Ch'ng

ABSTRACT

We report a previously undocumented drug interaction between cyclosporine A and quinine. A 39 year old Asian with a recent renal transplant was diagnosed to have a mild cerebral falciparum malaria. He was treated with seven days of oral quinine (600mg, 8 hourly), followed by a stat dose of pyrimethamine (75mg) - sulfadoxime (1200mg) because of a strong suspicion of chloroquine resistant falciparum malaria. Using a polyclonal radioimmunoassay method, we measured morning trough cyclosporine A level before, during and after the quinine treatment. Results showed a gradual decrease in the cyclosporine A level from a baseline value of 328 ng/ml to 107 ng/ml after seven days of oral quinine with a subsequent rise to pre-treatment level after discontinuation of quinine. There was no significant change in the dose of cyclosporine A administered during the period of quinine treatment (4.05 to 3.83 mg/kg body weight). Biochemical liver function tests, serum creatinine and hematological parameters were also essentially unchanged during this period. In vitro study showed no significant methodological interference in the cyclosporine assay by quinine dihydrochloride. These findings suggest an in vivo drug interaction between cyclosporine A and quinine. The mechanism of this interaction is not clear. Further studies are required to confirm the significance of this observation. Quinine and its stereoisomer, quinidine should be used with caution until further information is available.

Keywords : Drug interaction, cyclosporine, quinine, kidney transplant, falciparum malaria

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INTRODUCTION

During the past decade, cyclosporine A has become a widely used immunosuppressive drug in clinical transplantation. The dosage is usually adjusted according to blood cyclosporine levels so as to avoid overdosing and underdosing as this could lead to the undesirable complications of drug toxicity and inadequate immunosuppression respectively. Drug interactions with cyclosporine are therefore important as this could alter dosage requirements of cyclosporine. Many significant drug interactions had been documented in the past few years. We report here a possible drug interaction between cyclosporine and quinine.

CASE HISTORY

A 39 year old man with end stage renal failure, had a successful renal transplant two months previously. Ten days before admission, he developed lethargy, severe giddiness with tinnitus, nausea but no vomiting. There was no other significant history. Physical examination revealed an afebrile, rational and mentally orientated man. Pulse was 90/min and the blood pressure was 120/80 mmHg supine and standing. Heart, lungs, abdomen and the transplanted kidney were normal. Apart from a prominent horizontal jerk nystagmus, there were no significant funduscopic, auroscopic or neurological findings.

Department of Medicine
University Hospital
University of Malaya
59100 Kuala Lumpur
Malaysia

H W Tan, MBBS, MRCP
Lecturer

Department of Pathology
University Hospital
University of Malaya

S L Ch'ng, MBBS, MRCPath, FRCPA
Associate Professor

Correspondence to : Dr H W Tan

His medications were liquid cyclosporine A 75 mg twice daily, (Table 1), azathioprine 100 mg daily, prednisolone 20 mg daily and ranitidine 150 mg twice daily. Laboratory tests showed a blood Hb of 9.5 gm/dl, TWBC of 5800/ul, platelet of 234,000/ul.

Table I. Cyclosporine A dose and blood cyclosporine A level

Day	CyA[a] Dose mg/day	Body Wt Kg	CyA dose mg/kg	CyA level ng/ml	creatinine umol/L
0[b]	150	37	4.05	328	109
1	150	37	4.05	242	116
2	150	37	4.05	236	121
3	150	37.5	4.0	154	120
4	150	37.8	3.96	182	130
6[c]	150	38.5	3.89	107	115
7	150	39.1	3.83	124	117
9	200	39.7	5.03	142	110
25	250	49	5.1	363	129

a : cyclosporine
b : day quinine was started and shows baseline results.
c : day quinine was stopped after the evening dose.

The peripheral blood film revealed trophozoites of *Falciparum malaria* parasite in 0.3% of the erythrocytes. Urinalysis was normal. Chemical pathological investigation showed plasma urea of 10.8 mmol/L; creatinine, 109 umol/L; sodium, 134 mmol/L; potassium, 4.0 mmol/L; chloride, 103 mmol/L; albumin, 35 gm/L; globulin, 37 gm/L; aspartate aminotransferase, 18 iu/L; alanine aminotransferase 11 iu/L; alkaline phosphatase 99 iu/L; bilirubin, 5 umol/L; calcium, 2.28 mmol/L; inorganic phosphate, 0.8 mmol/L, prothrombin time ratio, 1.08. The brainstem auditory evoked potential test was normal.

A diagnosis of mild cerebral malaria was made. He was treated with oral quinine, 600 mg 8 hourly for a period of 7 days. This was followed by a single dose of three tablets of Fansidar (pyrimethamine 25mg and sulfadoxime 400mg). Quinine-Fansidar regimen was used because chloroquine resistant malaria is endemic in Peninsular Malaysia[1]. His symptoms subsided gradually over a period of 10 days. The parasitemia cleared within 4 days. We measured morning trough whole blood cyclosporine A level using a polyclonal radio-

immunoassay (RIA) method, (Cyclotrac kit produced by Incstar, USA) before, during and after the anti-malarial therapy.

RESULTS AND DISCUSSION

Table I shows a gradual decrease in the trough whole blood cyclosporine A level during quinine treatment, with a subsequent rise after discontinuation of quinine. His baseline cyclosporine A level (328 ng/ml) was within the therapeutic range of between 200 - 500 ng/ml. Although his weight gain was considerable, most of the increase was after the first week. During the course of his malaria treatment, there was no significant change in the dose of cyclosporine A, or in his serum creatinine (Table I), biochemical liver function tests and haematological parameters. No other drugs, except those mentioned, were given to him and he tolerated them well.

In vitro interference study on the cyclosporine RIA methodology was carried out as follows. Pooled plasma from 30 bone marrow transplant patients who were treated with cyclosporine A were obtained. The pooled sample was divided into two portions, of which one was spiked with quinine dihydrochloride (obtained from Halewood Chemical Ltd, Middlesex, England : 2 mls contain 600 mg of quinine dihydrochloride), to give a final quinine concentration of 10 mcg/ml. This is to approximate the average concentration of 7 mcg/ml obtained after chronic daily administration of one gram of quinine[2]. The spiked and unspiked samples were assayed in quadruplicate for cyclosporine A using the Cyclotrac kit. The results were 145 ± 7 ng/ml and 136 ± 6 ng/ml respectively. The spiked samples showed a slightly higher mean value than the unspiked samples and could be attributed to within assay variation (Table II).

The above clinical and laboratory data strongly suggest that the decrease in trough cyclosporine A level was due to an in-vivo drug interaction between cyclosporine A and quinine. The mechanism of this drug interaction is not clear. Quinine could interfere with the bioavailability of cyclosporine A or increase its clearance. Further studies are required to help confirm this.

Table II. Calculated within assay % error* based on two batches of routine cyclosporine A assays

Assay one		Assay two	
Cy A** ng/ml	Coef Var*** %	Cy A ng/ml	Coef Var %
57	29.0	45	26.6
108	15.3	89	14.0
160	10.8	134	9.9
215	8.6	182	7.8
274	7.3	236	6.7
339	6.5	361	5.5
493	5.8	436	5.2

* The data was processed using a computer program to calculate parameters for the four parameter logistic using 2+2 linear regression approach, developed by P Munson, D Rodbard, ML Jaffe, National Institute of Health, USA. (A gift from Prof. Rodbard).

** Cyclosporine A

*** Coefficient of Variation

With more transplants now being performed in countries where chloroquine resistant malaria is endemic, this drug interaction can have important implications in the interpretation of whole blood cyclosporine A level. It should also be noted that there had been no report on a drug interaction between cyclosporine A and quinidine which is a stereoisomer of quinine. Use of this drug combination should be monitored carefully until further information is available.

REFERENCES

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BOOK REVIEW

DIETARY IMBALANCES, METABOLISM AND DISEASE: THE SOUTHEAST ASIAN PERSPECTIVE

by John Candlish

Published by Singapore University Press, 1990

As the title implies, this book attempts to inject the Southeast Asian perspective into the relationships between dietary intake and metabolic disorders/diseases.

Taking into account the general paucity of data in Southeast Asia, the author has managed to put together an impressive account of the dietary and disease patterns of Southeast Asians and review them in the light of existing knowledge (mainly from the West).

Comparisons between the Western and Southeast Asian cuisines were made where relevant and some hypothesis drawn regarding the influence of the Southeast Asian diet on the various metabolic diseases/disorders. These diseases/disorders included coronary heart disease, diabetes, obesity, alcohol-related disorders, cancers, vitamin deficiencies and mineral deficiencies.

Concepts and controversies surrounding the intake and metabolism of dietary fat, cholesterol, fibre, sugars and proteins were explored together with their possible interactions with the above mentioned diseases/disorders.

The reader will become acutely aware of the need for further research on the changing dietary patterns of Southeast Asians, especially in the face of rapid urbanisation and economic growth, and how these can be harnessed for health promotion and disease prevention.

This is a useful book for doctors, nutritionists, dietitians and health educators interested in promoting health through diet but often frustrated by the apparent lack of scientific data relevant to the local scene.

Dr Mabel Teo
Food & Nutrition Department
Ministry of Health