Amplification of Quinine Cardiac effect by The Resistance-Reversing Agent Prochlorperazine in Falciparum Malaria.

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Abstract **The potential toxicity of "reversing agent" treatment was assessed in patients receiving quinine for falciparum malaria. The QTc interval, an electrocardiographic (EKG) marker of quinine effect, was measured every 30 min in 6 patients receiving intravenous quinine alone and in 6 patients receiving quinine with the resistance-reversing agent prochlorperazine (Compazine,® Stemetil).® Prochlorperazine (PC) alone was given to 6 healthy Thai volunteers. Compared to baseline values, the QTc interval was prolonged 30, 60, 90 and 120 minutes after PC injection in patients who got both drugs ($p<0.05$). The QTc interval was unchanged with quinine alone ($p>0.2$) and shortened after PC alone. EKG changes could not be explained by variations in either PC or quinine blood levels. Plasma PC levels did not correlate with the QTc interval ($p>0.2$) and neither total nor free quinine plasma levels rose after the injection of PC. Only benign effects of the antimalarial drug quinine were amplified by the reversing agent PC in this investigation, but the data clearly indicated that resistance - reversing therapy could amplify other, more dangerous, drug effects. Potential toxicity must be considered before using reversing agents to treat malaria or cancer.**

บทคัดย่อ ความเป็นพิษของการรักษาด้วย reversing agent ถูกประเมินในผู้ป่วยที่ได้รับ quinine สำหรับรักษา falciparum malaria, EKG marker ของผลจาก quinine (QTc) ถูกวัดทุก ๆ 30 นาที ในผู้ป่วย 6 คนซึ่งได้รับ quinine V อย่างเดียว และ 6 คนซึ่งได้รับ quinine + ยาที่เปลี่ยนความต้านยาของเชื้อ Prochlorperazine (Compazine, Stemetil) มีอาสาสมัคร 6 คน ได้รับ Prochlorperazine (PC) อย่างเดียว เมื่อเปรียบเทียบกับค่าปกติแล้ว QTc จะนานขึ้นเป็น 30,60,90 และ 120 นาที หลังจากฉีด PC ในผู้ป่วยที่ได้ยาทั้ง 2 ชนิด ($P<0.05$) QTc จะไม่เปลี่ยนแปลงในพวกที่ได้ quinine อย่างเดียว ($p>0.2$) และจะสั้นลงหลังจากได้รับ PC อย่างเดียว การเปลี่ยนแปลงทาง EKG ไม่สามารถอธิบายได้จากการแปรปรวนในระดับของ PC หรือ quinine ในเลือดอย่างหนึ่งอย่างใดระดับ PC ในพลาสมาไม่สัมพันธ์กัน QTc ($P>0.2$) และไม่สัมพันธ์กับระดับ quinine ในพลาสมา (free form และ total levels) ที่จะสูงขึ้นหลังฉีด PC จากการทดสอบนี้มีเพียงผลที่ไม่สำคัญนักของ quinine ที่ถูกทำให้มากขึ้นโดย PC แต่ข้อมูลต่าง ๆ ชี้ให้เห็นอย่างชัดเจนว่ายา PC จะไปเพิ่มผลของ drug effects ซึ่งจะเป็นอันตรายยิ่งขึ้น ดังนั้น ความเป็นพิษเหล่านี้ควรจะต้องถูกพิจารณาก่อนจะใช้ยาเหล่านี้ในการรักษา malaria หรือมะเร็ง (reversing agent = prochlorperazine (PC) = ยาที่เปลี่ยนความต้านทานยาของเชื้อ)

การเพิ่มฤทธิ์ของควินินต่อหัวใจในกรณีที่ใช้โปรคลอเปอราซีนร่วมด้วย

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Introduction

Infection with drug-resistant strains of *Plasmodium falciparum* is a growing public health problem in most malaria-endemic areas. Mechanisms of resistance remain poorly understood, but some resistant parasites have the ability to rapidly export antimalarial compounds, thereby reducing both drug accumulation and susceptibility to drug effects.[1] Quick drug release is one of several features resistant malaria shares with drug-resistant cancer cells, in which efflux is mediated by a transport protein, p-glycoprotein.[2,3]

A new approach to malaria treatment is to reverse resistance by using calcium antagonists and other "reversing agents" to block the parasite's drug pump.[4] Unfortunately normal human tissues

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also have p-glycoprotein[3,5]- perhaps to pump harmful substances out of cells. Combining an antimalarial drug with a reversing agent might therefore produce the desirable effect of concentrating drug within the parasite but also might have the undesirable effect of concentrating it inside the host's normal tissue. Three different reversing agents increased intracellular concentrations of chloroquine in cultured hepatocytes[6] and when mice were given the anticancer compound vincristine with the reversing agent verapamil, vincristine tissue levels were raised and there were more deaths than in mice given vincristine alone.[7]

We therefore tried to objectively and safely evaluate the potential toxicity of "reversing agent" treatment in patients receiving quinine for falciparum malaria. Potential toxicity was gauged by delays in myocardial repolarization, manifested by a prolonged QTc interval on the electrocardiogram (EKG). This benign EKG change occurs in some patients at therapeutic plasma quinine levels.[8-10] Serial QTc interval determinations were made in patients receiving quinine alone and compared with values obtained in patients receiving a combination of quinine and prochlorperazine (compazine^{R}, stemetil^{R}), a commonly used antiemetic drug with reversing agent properties. Our intent was to determine if prochlorperazine (PC) would amplify the electrocardiographic effects of quinine.

Patients and Methods

Volunteer patients with uncomplicated falciparum malaria who required parenteral therapy, usually because of vomiting, were randomly assigned to receive one of two regimens by a computer-generated random numbers list. The first regimen (Q) was a constant rate infusion of quinine dihydrochloride given as 7mg per kg of body weight over 30 min followed by 10mg of salt/kg of body weight over 4 h.[11] The second regimen (QP) included an identical infusion of intravenous quinine but, in addition, 12.5 mg of PC was given intramuscularly 2.5 h after the quinine infusion had begun. A control group of healthy Thai male volunteers received a single intramuscular injection of 12.5 mg PC alone.

EKGs were performed prior to therapy and at 30 min intervals thereafter. The EKG was run at twice normal speed (paper speed 50 mm per second) to permit more accurate measurement of the QT interval, which was corrected for heart rate by Bazett's formula.[12] Patients were questioned hourly about quinine side effects. Clinical status and vital signs were assessed every 30 min.

Plasma quinine levels were measured every half hour by a benzene extraction fluorescence method.[13] Free (non-protein bound) quinine was measured in ultrafiltrate after plasma was passed through an Amicon YMB system.[14] Specimens for PC were taken every half hour for 2h after the drug was given, stored at $-70°C$ protected from light, and assayed for PC by high performance liquid chromatography with electrochemical detection.[15]

Clinical and laboratory findings on admission were compared by the Student's t test for values normally distributed and by the Mann-Whitney U test for values not normally distributed. QT intervals at 3.0, 3.5, 4.0, and 4.5 h were compared by the paired Student's t test to the QTc interval at 2.5h (the time when prochlorperazine was administered to the QP group). Spearman's rank test was used to correlate QTc intervals with plasma PC levels. Two-tailed tests of significance were calculated in all cases.

Results

Randomization was successful ; there were no significant differences between treatment groups on admission with the exception of higher mean serum albumin levels in the Q group ($p<0.05$; Table 1) ; individual albumin levels however were all within normal range.

The QTc interval measured 2.5h after beginning quinine was longer than the corresponding pretreatment interval in every patient. At 2.5h, half the malaria patients received intramuscular PC and half did not ; the quinine infusion continued in both groups. Compared to baseline values at 2.5h, there was further QTc prolongation 30, 60, 90 and 120 minutes after PC injection in the QP group ($p<0.05$; Figure 1a). The QTc interval did not change in the Q group ($p>0.2$; Figure 1a) and became significantly shorter 60, 90, and 120 minutes after PC injection in the 6 normal volunteers who received PC alone (Figure 1a).

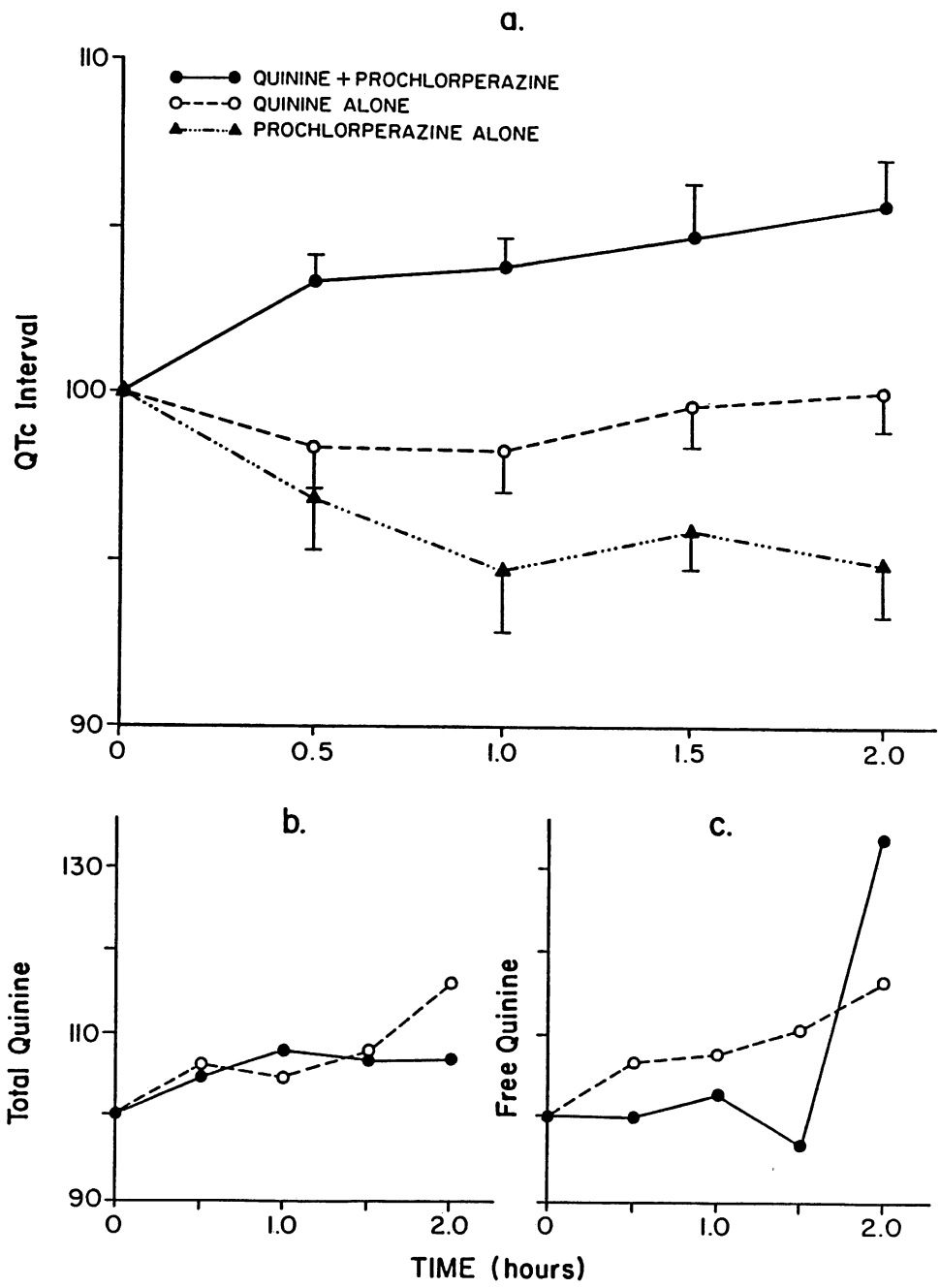

Figure 1. *Changes in the QTc interval after treatment with either quinine and prochlorperazine (QP), quinine alone (Q) or prochlorperazine alone (PC) are shown in 1a. Serial total and free quinine plasma levels are plotted in 1b and 1c, respectively. All measurements are expressed as percentage of a baseline value (± SEM) determined after 2.5h of quinine infusion (groups QP and Q) or immediately prior to prochlorperazine injection (group PC). Note the progressive prolongation of the QTc interval in the QP group and the lack of correlation between the QTc interval and quinine levels.*

The prolongations of myocardial repolarization in the QP group could not be explained by a PC-quinine interaction affecting either total or free quinine plasma levels (Figures 1b, 1c respectively). The concentration-time curves for total and free quinine in the QP patients were similar to those in the Q group, and quinine concentration curves differed markedly from QTc curves (Fig 1). Similarly, plasma PC levels did not correlate with QTc intervals during the 2h following PC infection ($p > 0.2$; Table 2).

No serious side effects or toxicity occurred in either the 12 malaria patients or the 6 healthy volunteers. Standard treatment with oral quinine (650mg PO q8h) and tetracycline (250mg PO q.i.d.) was begun as soon as patients were able to tolerate oral medication and produced clinical and parasitological cures in every case.

Table 1. Comparability of the Study Groups on Admission

Characteristic (Mean ± SEM)	Quinine Alone (n = 6)	Quinine plus Prochlorperazine (n = 6)	P
Clinical			
Age (years)*	27 (18-31)	31 (24-35)	>0.1
Weight (kg)	58.1 ± 1.5	56.3 ± 3.5	>0.1
Parasitemia (per mm^3)	16,413 ± 4,423	16,637 ± 4,487	>0.1
Biochemistry			
Total Protein (g/dl)	7.5 ± 0.1	7.4 ± 0.1	>0.1
Serum Creatinine (mg%)	0.9 ± 0.0	0.9 ± 0.1	>0.1
Serum Albumin (g/dl)	4.4 ± 0.1	3.9 ± 0.1	<0.01
Serum AST (Karmen Units)	22 ± 3	25 ± 4	>0.1
Serum ALT (Karmen Units)	18 ± 2	24 ± 3	>0.1
Hematology			
Packed RBC volume (ml/dl)	41 ± 1	38 ± 2	>0.1
Leucocytes ($X10^3$)	7.4 ± 0.9	5.7 ± 0.6	>0.1
Platelets ($X10^3$)	199 ± 11	209 ± 39	>0.1

Median (range)

Table 2. Relationship Between Plasma Prochlorperazine (PC) Level and QTc Interval in 6 Patients Receiving PC and Quinine.

Minutes After PC	30	60	90	120
Median Plasma PC Level (ng/ml) (range)	4.3 (2.1-5.9)	3.8 (2.3-5.4)	4.2 (2.1-5.4)	4.0 (1.9-4.6)
QTc Interval (% of value measured before PC injected)	105%	108%	107%	107%
Correlation Coefficient (r value)*	0.77	0.14	0.09	0.43
Significance of Correlation (p value)	0.2	0.5	0.8	0.2

**Spearman's rank correlation between the QTc interval and the plasma PC level*

Discussion

The rationale for the use of "reversing agents" in malaria centers on similarities between multidrug resistance in *Plasmodium falciparum* infection and that in tumor cells, where resistance is mediated by a transport protein product of the multidrug-resistance *(mdr1)* gene.[2,3] There is evidence both for and against a role for *mdr*-like genes in resistant *P. falciparum* infection.[14,17] The possible harmful effects of reversing agent therapy are of concern in both malaria and neoplasia, but are difficult to differentiate from underlying pathology in cancer patients. These individuals are often elderly with multiple medical problems, have extensive primary or metastatic disease, and are receiving relatively toxic drugs. The majority of malaria patients however are young and previously healthy.

Results of our study extend observations from in vitro and animal work which suggest that reversing agent therapy is potentially dangerous.[4,7] Prochlorperazine (PC) clearly amplified the delays in myocardial repolarization which commonly accompany quinine treatment. The mechanism(s) by which EKG changes were potentiated by PC cannot be stated with certainty. Quinine levels did not rise after PC was injected (Figure 1b), indicating that QTc interval prolongation was not mediated by PC-induced changes in quinine disposition. Serum albumin levels were lower in the QP group (Table 1), raising the possibility that there was more "biologically active" unbound drug in these individuals. However this was not the explanation for QTc interval prolongation. Patients in the QP group tended to have lower, rather than higher, levels of free quinine (Figure 1c).

It is unlikely that PC by itself produced the EKG changes. QTc interval prolongation is a prominent toxic effect of some phenothiazines, particularly piperidine phenothiazines such as thioridazine.[18] PC however is a piperazine phenothiazine, which are not noted for cardiac effects. PC plasma levels were not correlated with the QTc interval in our patients (Table 2) and PC given alone to healthy Thai controls shortened myocardial repolarization (Figure 1a).

How did the administration of PC lead to lengthening of the QTc interval ? One possibility is that PC slows the extrusion of quinine from cardiac tissue, perhaps by inhibition of an export pump such as p-glycoprotein. There is no direct

evidence from our study implicating this mechanism, but the data do rule out several other possible explanations, leaving interference with normal tissue export as plausible an explanation as any. PC reversed quinine resistance in cultured falciparum parasites (D. Kyle, Division of Experimental Therapeutics, personal communication), presumably by inhibition of the parasite drug pump.

We focused on a benigh EKG effect of quinine as a marker of potential toxicity, but the data indicate that reversing agents have the potential to amplify other, more dangerous, antimalarial drug effects. The possibility that inhibition of p-glycoprotein might increase the toxicity of drugs in normal tissues is now supported by clinical evidence.[19] Concerns about potential toxicity are particularly important now that clinical trials of reversing agent therapy have begun.[20]

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จาก

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