Ocular Side Effects of Chloroquine in Patients with Rheumatoid Arthritis, Systemic Lupus Erythematosus and Scleroderma

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Objective: *Ocular complication is a major long term adverse event of chloroquine. The present study was carried out to determine the ocular side effects of chloroquine in patients with rheumatic diseases.*
Material and Method: *Medical records of patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and scleroderma (Scl), who received chloroquine for their treatment, at the Division of Rheumatology, Faculty of Medicine, Chiang Mai University between 1 January 1992 and 31 August 2005 were reviewed. Only patients who were older than 16 years, had a clear total accumulative dose and duration of chloroquine therapy, and a regular ophthalmologic examination by ophthalmologists were included in the present study.*
Results: *One hundred and thirty-nine patients (54, 49, and 36 cases of RA, SLE and Scl, respectively) were studied. Forty-eight patients (34.5%) had ocular adverse effects (retinopathy in 37 and corneal deposition in 13 while two patients had both defects). There was no statistical difference in age, mean lean body weight adjusted daily dose, total dosage, and duration of treatment between those with and without ocular side effects. However, those with ocular side effects had significantly lower creatinine clearance (66.9 $\pm$ 26.9 vs 72.3 $\pm$ 20.0 ml/min, p = 0.046).*
Conclusion: *Ocular side effects of chloroquine were more common in patients with connective tissue diseases who had decreased creatinine clearance. The use of chloroquine in patients with impaired renal function should be of greater concern.*

Keywords: *Chloroquine toxicity, Retinopathy, Systemic lupus erythematosus, Rheumatoid arthritis, Scleroderma*

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Chloroquine is an antimalarial drug that is widely used for treatment of mucocutaneous and musculoskeletal problems in many connective tissue diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and scleroderma (Scl). The mechanisms of action of chloroquine are not clearly understood. Chloroquine can interfere with intracellular functions, inhibits enzyme activity, has anti-inflammatory activity, and effects immune functions[1]. The drug is rapidly absorbed after oral administration, and distributes extensively in body tissues, particularly in pigmented eye tissue, resulting in ocular toxicity. Chloroquine associated ocular side effects can be divided to three categories; 1) accommodation abnormality, which is the most common; 2) corneal deposition, and 3) pre and true-retinopathy. The accommodation defect, corneal deposition, and pre-retinopathy are in general completely reversible with drug discontinuation. On the other hand, "Bull's eye retinopathy" is a major concern as it has irreversible damage[1,2].

In Thailand, chloroquine is more widely used than hydroxychloroquine, which is another antimalarial drug that has lower ocular toxicity, but is much more expensive[1,3-6]. Therefore, the possibility of seeing chloroquine associated ocular toxicity should not

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be uncommon. However, study on the prevalence of chloroquine associated ocular toxicity in Thailand is limited[7].

The present study was performed to determine the prevalence of chloroquine associated ocular toxicity and compare the clinical characteristics between patients with and without ocular toxicity.

Material and Method

A review of the medical records of patients with SLE, Scl and RA receiving chloroquine as a part of their treatment was carried out. All patients were followed up at the Rheumatic Clinic, Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University. The period of the present study was from 1 January 1992 to 31 August 2005. Patients with RA, SLE, and Scl were defined by the diagnostic criteria developed by the American College of Rheumatology[8-11]. It was the authors' routine practice to send all patients receiving antimalarial drugs (either chloroquine or hydroxychloroquine) to ophthalmologists annually for monitoring of ocular side effects. For those older than 60 years, ocular examination was carried out every 6 months. Only patients older than 16 years with a clear starting date of chloroquine therapy, definite duration of chloroquine treatment, and clearly defined total dosage were included in the present study. Those who did not have regular ocular examinations by ophthalmologists, according to the schedule, were excluded.

In the present study, accommodation defects referred to the inability of the patients' eye to focus on objects. Corneal deposition referred to deposition of tiny white or yellow brown pigments in the cornea epithelium (Fig. 1). The retinopathy referred to pathology of the retina, which was graded according to the severity of the disease. The early retinopathy (reversible retinopathy) included macular edema, irregularity or mottling in the retina pigmentation, and lost foveal reflex. The Bull's eye retinopathy, or advanced retinal toxicity or irreversible retinopathy, referred to a central patchy area of macula depigmentation surrounded by a concentric ring of pigmentation (Fig. 2).

Clinical demographic data including age, sex, clinical diagnosis, body weight, total dosage of chloroquine, mean lean body weight adjusted daily dose, duration of treatment, and ocular side effects were recorded. Creatinine clearance was calculated by the Cockcroft-Gault method. The present study was approved by the Ethics Committee of the Faculty of Medicine, Chiang Mai University.

Statistical analysis

Categorical variables were shown as percent and continuous data were presented as mean $\pm$ standard deviation (SD). Comparison of continuous variables was determined by the student t test or Mann-Whitney U test, where appropriate. Pearson ^{2} test or Fisher exact test was used for comparison of categorical variables. Statistical analyses were performed with SPSS 11.0 for windows (SPSS Inc., Chicago, IL). A p-value of < 0.05 was considered statistically significant.

Results

There were 139 patients (123 females and 16 males) with a mean age $\pm$ SD and body weight of 39.8 $\pm$ 13.7 years and 47.9 $\pm$ 9.5 kg, respectively. Their mean total chloroquine dosage, mean lean body weight

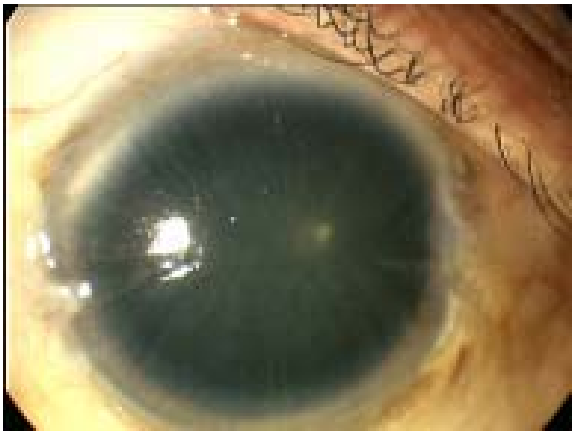

Fig. 1 Corneal deposition

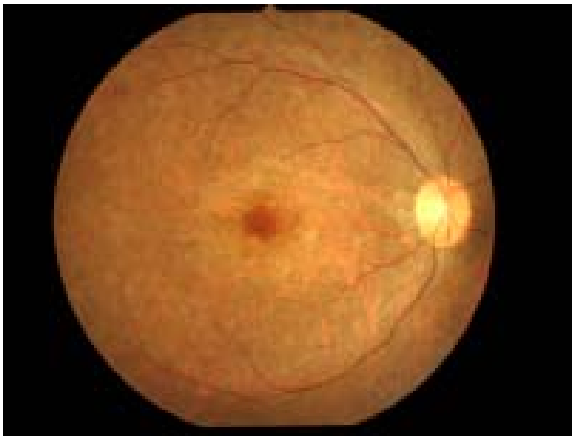

Fig. 2 Bull's eye retinopathy

Table 1. Clinical characteristics between the normal group and ocular side effect group

Clinical variables	Normal Group n = 91	Ocular toxicity Group (corneal and retinal deposition) n = 48	p-value*	Corneal deposition Group n = 13	p-value*	Retinopathy Group (early and Bull's eye) n = 37	p-value*
Clinical diagnosis							
-RA	29	25		3		22	
-SLE	38	11		3		8	
-Scleroderma	24	12		7		7	
Sex (F:M)	8.1:1	7:1	0.786	12:1	1.000	6.4:1	
Mean age (yrs)	39.2±12.9	42.2±14.1	0.128	45.4±19.7	0.306	41.19±11.9	0.293
Body weight (kg)	47.8±8.3	48.2±11.5	0.719	45.4±9.7	0.248	48.8±11.8	0.966
Mean lean body weight adjusted daily dose (mg/kg/day)	4.0±1.3	4.3±1.4	0.301	4.9±1.3	0.035	4.07±1.36	0.942
Mean cumulative dose of chloroquine (gm)	189.7±131.9	184.1±104.6	0.666	142.4±92.1	0.343	205.1±101.2	0.286
Mean duration of chloroquine use (months)	38.1±31.3	35.6±20.9	0.661	24.8±20.4	0.140	39.3±19.4	0.164
Mean serum Cr (mg/dl)	0.83±0.17	0.93±0.29	0.160	0.9±0.2	0.203	0.91±0.31	0.406
Mean serum CrCl (cc/min)	72.3±20.0	66.9±26.9	0.046	61.1±27.6	0.035	68.9±26.5	0.191

Data are expressed in mean ± SD
* Unpaired t test and Mann Whitney U test

adjusted daily dose, duration of treatment, and serum creatinine clearance was 189.2 ± 123.2 gm, 4.1 ± 1.3 mg/kg/day, 37.3 ± 28.1 months, and 71.0 ± 22.7 ml/min, respectively. The diagnosis was RA, SLE and Scl in 54 (38.8%), 49 (35.3%), and 36 (25.9%) cases, respectively. The ocular side effects were seen in 48 patients (34.5%). There was retinopathy in 37 cases (26.6%) and corneal deposition in 13 (9.4%). Two patients had both defects.

Table 1 summarizes the clinical characteristics between the normal group and those with ocular side effects. When comparing patients with and without ocular side effects (corneal deposition and retinopathy), there was no statistical difference in age, mean lean body weight adjusted daily dose, total dosage, and duration of treatment. However, patients with ocular side effects (corneal deposition and retinopathy) had significantly lower creatinine clearance than those without (66.9 ± 26.9 vs 72.3 ± 20.0 ml/min, p = 0.046). Patients with corneal deposition also had significantly lower creatinine clearance (61.1 ± 27.6 vs 72.3 ± 20.0 ml/min, p = 0.035) and received a higher mean lean body weight adjusted daily dose of chloroquine than the normal group (4.9 ± 1.3 vs 4.0 ± 1.3 mg/kg/day, p = 0.035).

In the retinopathy group, there was no statistical difference in age, mean lean body weight adjusted daily dose, mean total dosage, and creatinine clearance when compared with the normal group. The retinopathy could occur as early as 9 months after starting chloroquine treatment.

While 37 patients had retinopathy, five had not been graded for severity; therefore, 32 cases were analyzed. Table 2 compares the clinical features of 29 early retinopathy and three Bull's eye retinopathy patients. There was no statistical difference in age, mean lean body weight adjusted daily dose, mean total dosage, and creatinine clearance between the two groups.

After cessation of chloroquine, eight of 22 patients (36.4%) with early retinopathy recovered completely, but 14 (63.6%) showed no change. One Bull's eye retinopathy patient had permanent damage, and the remaining two were lost to follow up.

Discussion

In the present study, the authors found that up to one-third (34.5%) of the Thai patients with connective tissue disease and receiving long term chloroquine treatment experienced ocular side effects. Retinopathy and corneal deposition were the common ocular side effects seen in 26.6% and 9.4%, respectively. No accommodation defect was found. The reason why the accommodation defect was not found in the present study was not clear, but it might be due to a reversible defect and the patients possibly not notifying the physicians.

The prevalence of retinopathy and corneal deposition from chloroquine has been studied in Thai patients with skin and connective tissue diseases, and these conditions were found in 14.2% and 9%, respec-

Table 2. Comparison of early retinopathy and Bull's eye retinopathy group

Clinical variables	Early Retinopathy Group n = 29	Bull's eye Retinopathy Group n = 3	p-value*
Diagnosis			
-RA	16 (55.3)	3 (100)	
-SLE	6 (20.6)	0 (0)	
-Scleroderma	7 (24.1)	0 (0)	
Sex (F:M)	6.3:1	2:1	
Mean age, (yrs)	41.7 ± 10.9	43.3 ± 15.9	0.816
Body weight (kg)	48.0 ± 9.3	64.0 ± 27.5	0.207
Mean lean body weight adjusted daily dose (mg/kg/day)	4.2 ± 1.1	2.9 ± 0.7	0.073
Mean cumulative dose of chloroquine (gm)	208.8 ± 105.5	228.1 ± 97.6	0.624
Mean duration of chloroquine use (months)	38.7 ± 19.0	46.7 ± 22.7	0.624
Mean serum Cr (mg/dl)	0.8 ± 0.2	1.1 ± 0.6	0.808
Mean serum CrCl (cc/min)	66.6 ± 15.0	92.6 ±76.3	0.855

Data are expressed in mean ± SD
* Mann Whitney U test

tively[7]. No correlation between age, sex, cumulative doses, duration of treatment, corneal deposition and retinopathy was identified. In Western countries, the prevalence of chloroquine-associated retinopathy varied from 0.001% to 40.0% depending on the inclusion criteria or the study designs[5,6,12]. Generally, the total cumulative dose and duration of treatment have been associated with retinopathy[5,13,14]. However, Mackenzie AH reported that the daily-adjusted dose to lean body weight of more than 4 mg/kg/day, and not the total cumulative dose or duration of chloroquine treatment, was associated with retinopathy[15]. Araiza CR, et al found that both mean daily dose and lean body weight daily-adjusted dose associated with retinopathy[16]. Moreover, age over 50 years, corneal deposition, and mean daily dose also increase the risk of chloroquine-associated retinopathy[12,16,17]. Most reported cases of chloroquine retinopathy received 250 mg or more as a daily dose for many months. The total accumulation of chloroquine for the development of chloroquine-associated retinopathy is difficult to define, but the risk may begin with a total cumulative dose of 100 gm or a dose of 250 mg/day that continues for more than a year[18].

In the present study, when compared with the normal group, the retinopathy group did not show a statistical difference in age, total cumulative dose, and mean lean body weight daily-adjusted dose. Early and late retinopathy also showed no statistical difference in those clinical data. However, the authors found that lower creatinine clearance and higher mean lean body weight daily-adjusted dose were more common in the corneal deposition and total ocular toxicity group (corneal deposition and retinopathy group).

The American Academy of Ophthalmology recommends a yearly ocular examination for high risk chloroquine-treated patients, who have a mean lean body weight daily-adjusted dose of more than 3 mg/kg/day, are aged over 60 years, have impaired renal or liver function, and had previous use of chloroquine[19]. It should be noted that the presented patients in the ocular toxicity group received a higher daily-adjusted dose of chloroquine than that recommended (mean 4.3 mg/kg/day). Therefore, the higher lean body weight daily-adjusted dose in those patients with impaired renal function was the main cause of chloroquine associated ocular toxicity in the present study.

There were several limitations in the present study. First, this was a retrospective study, therefore, some clinical and laboratory data might not have been recorded. Second, many cases were excluded from the present study as they did not have the exact date of chloroquine administration, and the total cumulative dose could not be calculated. Therefore, cases with ocular toxicity might have been missed and were not included in the present study, making the prevalence of ocular toxicity from chloroquine lower than it should be possible. Finally, the number of patients was small; this might have affected the statistical characteristic. A long term prospective study is needed to confirm the present study's findings.

As chloroquine retinopathy is a serious condition, a strategy to prevent irreversible damage is crucial. Careful adherence to the dosing guidelines (daily dose of < 3 mg/kg lean body weight) is recommended, and the dose should be re-evaluated on a regular basis according to the patient's body weight and renal and liver functions. Although an electro-oculogram is more sensitive in detecting retinal abnormality, it is complex, expensive and available only in some medical centers[20]. Periodic Amsler grid testing, color vision testing, and ophthalmoscopic examination can be used to detect early chloroquine retinopathy[21,22]. These tests are cheap, can be done in a general hospital and are suitable for developing countries.

Conclusion

Corneal deposition and retinopathy associated with chloroquine therapy tended to occur more in connective tissue patients who had decreased creatinine clearance. Dose adjustment in patients with impaired renal function should be of more concern as should regular ocular examination.

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การศึกษาผลข้างเคียงทางตาจากยาคลอโรควินในผู้ป่วยโรคข้ออักเสบรูมาตอยด์ โรคเอสแอลอี และโรคผิวหนังแข็ง

สุกัญญา ลี้เจริญ, ศุภราภรณ์ วังแก้ว, วรวิทย์ เลาห์เรณู

วัตถุประสงค์: *ภาวะแทรกซ้อนทางตาเป็นผลข้างเคียงที่สำคัญของการได้รับยาคลอโรควินในระยะยาว การศึกษานี้ทำขึ้นเพื่อศึกษาผลข้างเคียงทางตาจากยาในผู้ป่วยกลุ่มโรคข้อและรูมาติสซั่ม*

วัสดุและวิธีการ: *เป็นการทบทวนเวชระเบียนผู้ป่วยโรคข้ออักเสบรูมาตอยด์ โรคลูปัส และโรคผิวหนังแข็ง ที่ได้รับยาคลอโรควิน การรักษาโรคและติดตามการรักษาที่หน่วยโรคข้อ และรูมาติสซั่ม คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่ ตั้งแต่วันที่ 1 มกราคม พ.ศ.2535 ถึง 31 สิงหาคม พ.ศ.2548 ผู้ป่วยที่มีอายุมากกว่า 16 ปี และทราบปริมาณยาสะสม และระยะเวลาการได้รับยาที่แน่นอน และได้รับการตรวจตาอย่างสม่ำเสมอด้วยจักษุแพทย์เท่านั้นที่จะถูกคัดเลือกเข้าสู่การศึกษา*

ผลการศึกษา: *ผู้ป่วย 139 ราย (โรคข้ออักเสบรูมาตอยด์ 54 ราย, โรคเอสแอลอี 49 รายและโรคผิวหนังแข็ง 36 ราย) พบความชุกของผลข้างเคียงทางตาจากยาคลอโรควิน 48 ราย (ร้อยละ 34.5) โดยพบพยาธิสภาพที่จอตา 37 ราย พบการสะสมยาที่กระจกตา 13 ราย และพบร่วมกัน 2 ราย ไม่พบความแตกต่างระหว่างผู้ป่วยที่เกิดผลข้างเคียงและกลุ่มที่ไม่เกิดผลข้างเคียงทางตา ในด้าน อายุ ขนาดยาเฉลี่ยปรับตามน้ำหนักตัวต่อวัน ขนาดยาสะสม และระยะเวลาที่ได้รับยา แต่พบว่ากลุ่มที่เกิดผลข้างเคียงทางตา มีค่าการชำระครีแอทินินต่ำกว่ากลุ่มไม่เกิดผลข้างเคียงอย่างมีนัยสำคัญทางสถิติ (66.9 $\pm$ 26.9 เทียบกับ 72.3 $\pm$ 20.0 มิลลิลิตร/นาที, $p = 0.046$)*

สรุป: *พบการเกิดผลข้างเคียงทางตาจากยาคลอโรควินสูงขึ้นในผู้ป่วยโรคข้อและรูมาติสซั่มที่มีค่าการทำงานของไตลดลง จึงควรใช้ยาด้วยความระมัดระวังเพิ่มขึ้นในผู้ป่วยโรคไต*