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Chloroquine and eye problems at a general hospital in western Thailand

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ABSTRACT

Objective: This study aimed to explore the eye problems after CQ use, to review if the eye examinations were performed during patients were treated with CQ and to identify factors related to those eye problems. **Method:** Retrospective study was done. Data were collected from both electronic medical records and medical records. Patients who were treated with CQ during May15, 2010- May 31, 2019 at a general hospital in western Thailand were included. **Results:** There were 123 patients who were treated with CQ. Eye problems were found in 26 patients (21.14 %). Majority of those had blurred vision (13/26; 50.00%). Focus on having eye examinations, thirty-five patients received eye examinations during the period of taking CQ (28.46%). Factors related to eye problems were long duration of use, the cumulative amount of CQ and the number of systems involved in patient comorbidities. (*p-value* = 0.012, 0.007 and 0.046 respectively). **Conclusions:** Patients who were treated with CQ should receive regular eye examinations, especially patients who had factors related to eye problems.

Keywords: ADRs, adverse drug reactions, chloroquine maculopathy, chloroquine, eye problems, ocular problems

INTRODUCTION

Chloroquine (CQ) and its analog hydroxychloroquine (HCQ) have been used for the treatment and prophylaxis of malaria and successfully treat several infectious. The indications for CQ and HCQ have since been expanded to successfully and safely treatment rheumatological and other immunological diseases including rheumatoid arthritis and systemic lupus erythematosus (SLE).[1,2] CQ and HCQ had been evaluated in various trials to treat adult patients with COVID-19; however, it was not recommended, because CQ/HCQ has serious side effects.[3-8] Besides, headache, hepatitis, elevated liver enzyme, various skin eruptions, and gastrointestinal disturbances were also reported. The most severe side effects of CQ are cardiac toxicity.[8] This medication may also cause serious eye problems.[9,10] Eye problems occur after CQ use because CQ damages retina, especially among patients with a long-time use. Patients might be asymptomatic in early changes. In the early stage, if patients stop using CQ this symptom can be better. If the eye problems progress as CQ maculopathy, it is irreversible damage and can lead to vision loss. CQ maculopathy can progress even after the medication is stopped. The incidence of retinopathy from CQ was found higher than HCQ (66.7% vs. 9.5%).[4] The study at Ramathibodi Hospital in Thai population, it was presented that 20.63% (33 of 160) and 2.59% (20 of 773) had eye problems related to CQ and HCQ use, respectively.[11] However, it is preventable. Eye examination every 6–12 months is important for preventing permanent visual loss.[5,10] Boonyaprasert (2007) reported three cases of CQ long-term treatment at Phra-nakhon Si Ayutthaya hospital.[12] These patients had eye problems, blurred vision, and CQ maculopathy. It was found that there were two patients who had not been received any eye examination.

In Damnoen Saduak hospital a general hospital, in western Thailand, there is a limitation of resource such as ophthalmologists. There were only two ophthalmologists who had to examine all problems of eye diseases. The demand for ophthalmologists is quite high. American Academy of Ophthalmology (AAO)[10] recommended that patients treated with CQ to have eye examination every 6–12 months, but how eyes examination could be performed after CQ use with

hospital limitations. It was interesting about current situation of eye problems after CQ use and how it was managed. As the fact that hospital pharmacists not only can detect and report adverse drug reactions (ADRs) but help in the prevention of ADRs, working to understand the suspected ADRs such as eye problems after CQ use would provide useful information for proper patients' eye examination.[13]

CQ was prescribed to treat arthritis, connective tissue disorder, and others at Damnoen Saduak hospital. This is a 250-bed general hospital in Ratchaburi province, western Thailand. HCQ is not available in this hospital formulary. It may be helpful to survey the eye problems occurred in patients taking CQ to find out how to prevent further ocular adverse reactions in the future.

Objective

The objective of this study was to explore the eye problems after CQ use, to review if the eye examinations were performed during patients who were treated with CQ, and to identify factors related to those eye problems.

MATERIALS AND METHODS

Retrospective study was done by collecting 9 years backward data (2010–2019).

Participants

Patients who were treated with CQ at Damnoen Saduak hospital in Ratchaburi province, Thailand.

Inclusion Criteria

Patients who treated with CQ during May 15, 2010–May 31, 2019 were included in the study.

Exclusion Criteria

Patients who passed away and patients who were prescribed with CQ for only 1 time then referred to other hospitals, because there were incomplete data of CQ usage and eye problems were excluded from the study.

Definition

Eye problems were any abnormal eye symptoms, in which the physicians noted in either electronic medical record or medical record after CQ was prescribed.

The total amount of CQ (g) was defined as the amount of CQ that patient received from starting date to May 31, 2019. It was calculated by (number of pills received × 250)/1,000. Patients were assumed to have a good compliance. Consequently, total amount of CQ received equaled the cumulative amount of CQ use.

Duration of the treatment (day) was started from the 1st day that patient received CQ to May 31, 2019.

Eye examination data were data if patients had been referred to have eye examination or eye screening by ophthalmologists to detect eye problems. It was collected by the information written in medical records or recorded in the database.

Renal function divided into five stages according to the estimated glomerular filtration rate recommended by KDIGO guideline (2012).

Data Collection

Hospital database was applied to screen how many times pharmacy department dispensed CQ in the beginning. Data were managed to identify how many patients who received CQ during May 15, 2010–May 31, 2019. Electronic medical record and medical record of each patient were tracked. Data were collected dividing into four parts. Those were characteristics of the patient (gender, age, weight, underlying diseases, and renal function test), CQ usage (indication, amount, and duration), eye problems, and eye problems management. This study obtained ethical approval from the Ethics Committee for Human Research of Silpakorn University before the study initiation (COE 62.1024-028 Exp. Oct 23, 2020).

Statistical Analysis

Descriptive statistics were used to describe patient demographic and the occurrence of eye problems. Fisher's exact test, Pearson's Chi-square, and *t*-test were used to analyze the association between factors and those eye problems.

RESULTS

General Characteristics

There were 138 patients who were treated with CQ during 2010–2019. Fifteen patients were excluded from the study (seven patients passed away and eight were prescribed with CQ only 1 time and referred to other hospitals). Consequently, there were 123 patients who were treated with CQ and included in this study.

It was found that majority of the study group were female (110; 89.43%) and age <60-years-old (71; 57.72%). Rheumatoid arthritis was the main indication of CQ use 65; 52.85%) followed by SLE (39; 31.71%) and other indications (19 patients 15.45%). Those other indications were arthritis, scleroderma, and psoriasis. There were two patients who used CQ for more than one indication. One patient had rheumatoid arthritis and SLE and the other had rheumatoid arthritis and psoriasis. Most of patients had renal function in Stage 1–2 before (62; 50.41%) and after using CQ. (69; 56.10%). In this study, 85 patients (69.11%) who were treated with CQ had at least one system of comorbidity. The majority of comorbidity was cardiovascular disease (62; 50.41%) such as hypertension and cardiac arrhythmia. Each patient could have more than one underlying disease and more than one system of comorbidity.

Average total amount of CQ prescribed in this study was 167.54 ± 186.56 g (range: 0.5–792.5 g). Average duration of the treatment was around 4 years (1,416 ± 1,392.39 days; range: 1–5,803 days). The general characteristics of the patients are shown in Table 1.

Eye Problems

Eye problems were noted in 26 patients (21.14%). Fifteen patients were recorded having blurred vision (12.19%) and 11 patients were recorded having CQ maculopathy (8.94%), as shown in Table 2.

Table 1: General characteristics

Characteristics	*n*	% *(N=123)*
Gender		
Male	13	10.57
Female	110	89.43
Age		55.29±14.66
<60	71	57.72
≥60	52	42.28
Weight		57.14+13.92
Indication		
Rheumatoid arthritis	65	52.85
Systemic lupus erythematosus	39	31.71
Others	19	15.45
Missing data	2	1.63
Two patients had more than one indication of CQ prescribed.		
Renal function before using CQ		
Stage G1–G2	62	50.41
Stage G3a–G5	5	4.07
Renal function after using CQ		
Stage G1–G2	69	56.10
Stage G3a–G5	7	5.69
Comorbidity		
No comorbidity	38	30.89
At least one system of comorbidity	85	69.11
System of comorbidity*		
Cardiovascular diseases	62	50.41
Endocrinologic diseases	26	21.14
Ophthalmic diseases	10	5.56
Rheumatologic diseases	10	5.56
Renal diseases	9	5
Respiratory diseases	5	2.78
Neurologic diseases	4	3.25
Hematologic diseases	4	3.25
Immunologic diseases	3	1.67
Others (infection, reproductive system diseases, psychiatric, obesity, and gastrointestinal diseases)	10	8.13
Average total amount of CQ (g)		167.54±186.56 (0.5–792.5)
Average duration of treatment (days)		1,416.22±1,392.39 (1–5,803)

*Each patient could have more than one system of comorbidity.
CQ: Chloroquine

Factors Associated with Eye Problems

Twenty-six patients had eye problems. Most of them were female and aged equal or >60 years with average weight of 55.68 kg. The majority indication of CQ use was rheumatoid arthritis. Average total amount of CQ and duration of CQ treatment of patients with eye problems was 254.57 ± 203.91 g and 2,021.46 ± 1,566.19 days (around 5.5 years), respectively. Patients with eye problems had average total amount and duration of treatment more than those without eye problems. There was a 27-year-old woman who had eye problems only after 3 days of using CQ. She was only one patient with eye problem who aged <42. After an in-depth review, this patient had already received HCQ for treating his symptom, SLE, from another hospital before admitted as an in-patient at our study site.

Table 2: Eye problems

	n	% (n=123)
Not occurred	97	78.86
Occurred	26	21.14
Blurred vision	15	12.19
CQ maculopathy	11	8.94

Focus on factors associated with eye problems, it was found that the duration of treatment, the total amount of CQ, and the number of systems of patient comorbidity involved were statistically significant factors associated with eye problems (P = 0.012, 0.007, and 0.046, respectively). Eye problems tended to occur in patient who received CQ for a long time, having high total amount of CQ and those who had underlying disease involved in many systems. Majority of patients had eye problems earlier than 5 years of CQ treatment (14/123; 11.38%). Moreover, five patients (5/123; 4.06%) had eye problems within 1 year.

In the part of CQ indication, CQ was prescribed for two indications in two patients. There were also two patients who had no data of CQ indication. Evaluation of eye problems related to CQ indication was calculated separately by number of patients with each indication [Table 3].

Eye Examination after CQ Use

From database and medical records, there were 35 patients (35/123; 28.46%) who received eye examination by ophthalmologists after CQ use. Among 35 patients who were recorded receiving eye examination by ophthalmologists, there were nine patients who had eye problems (7.32%) [Table 4].

Management of Eye Problems

The information of how eye problems was managed, which was collected after CQ eye problems were found. It was found that 26 patients who had eye problems, CQ were discontinued in 13 patients (50%), and 9 cases were still taking CQ. (two cases with the same dose and seven with decreased dose). Another four patients referred to other hospitals.

After management, ocular symptoms were unchanged in seven patients and got worse in four patients. Only one patient who stop taking CQ got better. There were 14 cases whose had no data of follow-up [Table 5].

DISCUSSION

Pharmacists have a potential role in reporting, identifying, and preventing ADRs which lead to fast management. It is important for pharmacists to understand if eye problems occurred after CQ

Table 3: Factors associated with CQ ocular side effects

Factors	Eye Problems		*P*-value
	Occurred (*n*=26)	Not occurred (*n*=97)	
Gender			
Male	2 (1.63)	11 (8.94)	0.734†
Female	24 (19.51)	86 (69.92)	
Age	59.62±11.05	54.13±15.33	
<60 year	11 (8.94)	60 (48.78)	0.073††
≥60 year	15 (12.20)	37 (30.08)	
Average weight (kg)	55.68±13.44	57.57±14.1	0.544¤
Indication			
One indication	25	94	0.385†
Two indications	1	1	
Missing data	0	2	
Number of patients with each CQ indication.			
Rheumatoid arthritis	15 (12.20)	50 (40.65)	0.780††
Systemic lupus erythematosus	9 (7.32)	30 (24.39)	
Others	3 (2.44)	16 (13.01)	
Renal function before using CQ			
Stage G1–G2	13 (10.57)	49 (39.84)	0.310†
Stage G3a–G5	2 (1.63)	3 (2.44)	
Renal function after using CQ			
Stage G1–G2	17 (13.82)	52 (42.28)	0.371†
Stage G3a–G5	3 (2.44)	4 (3.25)	
Average duration of treatment (days)	2,021.46±1,566.19	1,248.81±1,308.24	0.012*¤
average±SD (range)	(3, 5,803)	(1, 5,137)	
Duration of treatment (years)			
<5 years	14 (11.38%)	71 (57.72%)	
5–10 years	8 (6.5%)	17 (13.82%)	
>10 years	4 (3.25%)	6 (4.88%)	
Average total amount of CQ (g)	254.57±203.91	144.21±174.40	0.007*¤
average±SD (range)	(1.5, 695.75)	(0.5, 792.5)	
Number of systems of comorbidity			
No comorbidity	6 (4.88)	32 (26.02)	0.046*††
One system	7 (5.69)	37 (30.08)	
Two systems	11 (8.94)	16 (13.01)	
≥3 systems	2 (1.63)	12 (9.76)	

*Statistically significant at $P<0.05$, †Fisher's exact test, ††Pearson Chi-square, ¤*t*-test, and CQ: Chloroquine

Table 4: Eye examination

Eye examination	Eye problems occurred	Eye problems not occurred	Total
Eye examined	9 (7.32)	26 (21.14)	35 (28.46)
No eye examined	17 (13.82)	71 (57.72)	88 (71.54)
Total	26 (21.14)	97 (78.86)	123 (100)

use. If patients take CQ and its analogs for a long time, they should have eye examination for screening the early sign of visual abnormalities.[2,10] If eye problems are found, it is recommended a cessation of CQ and its analogs. The discontinuation of CQ and its analogs might not prevent progression of retinopathy. However, the severity of CQ eye problems is less if they are recognized early.[5,10] In this study, there were two patients whose symptoms got worse after CQ cessation. However, there was 1 case got better after stop taking CQ. The eye problem presented in that case was only blurred vision.

In this study, CQ was prescribed to 123 patients at the local hospital, Thailand during 2010–2019 and 26 patients

Table 5: Management of eye problems and ocular symptom

Management related to CQ (%)	Better	Unchanged	Worse	No data available	Total
Discontinuation	1 (3.85)	4 (15.38)	2 (7.69)	6 (23.08)	13 (50)
Continuation (same dose)	0 (0)	0 (0)	1 (3.85)	1 (3.85)	2 (7.69)
Continuation (decreased dose)	0 (0)	3 (11.54)	1 (3.85)	3 (11.54)	7 (26.92)
Referral	0 (0)	0 (0)	0 (0)	4 (15.38)	4 (15.38)
Total	1 (3.85)	7 (26.92)	4 (15.38)	14 (53.85)	26 (100)

CQ: Chloroquine

(21.14%) had been noted having eye problems. All ocular symptoms were included, not only retinopathy. However, it was found that 11 patients were noted as CQ maculopathy (8.94%). Most of eye problems were recorded earlier than 5 years. It was consistent with Tangtavorn *et al*. (2016) study.[14] They studied incidences of and risk factors for CQ and HCQ retinopathy in Thai rheumatologic patients. Data were collected from patients who regularly underwent eye screening examinations. The result showed that CQ retinopathy was detected by ophthalmologists in 14 of 173 patients (8.09%) and most patients developed retinopathy earlier than 5 years.

In this study, the average age of patients who had eye problems was older than those who did not have eye problems. (59.62 + 11.05 vs. 54.13 + 15.33, respectively). Eye problems were found in patients at the age equal or older than 42 and there were four patients (4/26; 15.38%) who had eye problems during 1 years of CQ treatment (the 27-year-old patient who had eye problem in 3 days of CQ treatment was excluded, because she had received HCQ before from another hospital).

Many studies were performed by ophthalmologists to monitored CQ eye adverse effect, it showed that various factors were concerned.[9-10,15] In this study, number of systems involved in patients' comorbidities, duration, and total amount of CQ use were related to eye problems ($P = 0.046$, 0.012, and 0.007, respectively). It was consistent with Rujiwetpongstorn study (2015) which found that duration of treatment ($P = 0.028$) and cumulative dose ($P = 0.004$) was significantly related to maculopathy.[15] AAO (2016) summarized that high dose and long duration of the use are the most significant risks. Comorbidities as renal disease or use of tamoxifen were also important factors.[10] Patients' renal functions were not related to eye problems in this study. Moreover, the use tamoxifen was not evaluated. There was no previous study mentioned about the association between number of systems of comorbidity and occurrence of eye problems.

Pharmacist can provide information to prevent CQ eye problems. The result presented that eye problems were not found in patients who were younger than 40-years-old. Patients who were older than 42 years old should be recommended to receive eye examination during their 1st year of CQ treatment. Patients who received high dose of CQ for a long time and had comorbidities with many systems involved should be monitored closely, at least every 1 year.[2]

The limitation of this study was that it was retrospective research collecting patients' history from electronic hospital database and patients' records for 9 years (2010–2019). This study focused on eye problems during CQ usage. Data depended on what were recorded. Some eye problems were notified as CQ maculopathy, but there was no record of eye examination. Moreover, patients might have eye problems from other causes. Data were collected from only one general hospital, Thailand. Consequently, the external validity of this study is limited. Further, research would be more benefit from prospective study conducted to monitor how eye problems occur after patients receiving CQ.

CONCLUSION

All patients who had eye problems after CQ use in this study were older than 40 years old. Majority of them had eye problems within 1 year. Long-term use, high amount of CQ received, and many numbers of system of comorbidities were factors related to eye problems.

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REFERENCES

1. Chloroquine. In: Lexi-Drugs Online. Wolters Kluwer Health, Inc.; 2021. Available from: http://online.lexi.com. [Last accessed on 2021 Mar 19].
2. Thai Rheumatism Association. Clinical Practice Guideline (CPG) for Diagnosis and Treatment of Rheumatoid Arthritis. 2014. p. 34-40. Available from: https://www.thairheumatology.org/index.php/learning-center/for-physician/for-physician-3?view=article&id=73:1-29&catid=16 . [Last accessed on 2022 Mar 22].
3. World Health Organization (WHO). Hydroxychloroquine. In: WHO, editor. Therapeutics and COVID-19: Living Guideline, 20 November 2020. Geneva: WHO; 2020. p. 12-5.
4. Peng H, Chen Z, Wang Y, Ren S, Xu T, Lai X, *et al.* Systematic review and pharmacological considerations for chloroquine and its analogs in the treatment for COVID-19. Front Pharmacol 2020;11:554172.
5. Manolette RR, Barbara LR, Stephen CF. Chloroquine and hydroxychloroquine toxicity guidelines: Overview. Available from: https://emedicine.medscape.com/article/1229016-overview. [Last accessed on 2021 Feb 09].
6. Kaddoura M, AlIbrahim M, Hijazi G, Soudani N, Audi A, Alkalamouni H, *et al.* COVID-19 Therapeutic Options Under Investigation. Front Pharmacol 2020;11:1196.
7. National Institutes of Health (NIH). Coronavirus Disease 2019 (COVID-19) Treatment Guidelines 2020. Available from: https://www.covid19treatmentguidelines.nih.gov/. [Last accessed on 2021 Mar 26].
8. Acharya Y, Sayed A. Chloroquine and hydroxychloroquine as a repurposed agent against COVID-19: A narrative review. Ther

Adv Infect Dis 2020;7:1-14.
9. Kurathong S. What's new in "hydroxychloroquine retinopathy". Vajira Med J 2018;62:53-62.
10. Marmor MF, Kellner U, Lai TY, Melles RB, Mieler WF, American Academy of Ophthalmology. Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). Ophthalmology 2016;123:1386-94.
11. Vilainerun N, Hanutsaha P. Patterns of hydroxychloroquine and chloroquine retinopathy in Thai patients. Thai J Ophthalmol 2019;33:66-75.
12. Boonyaprasert K. Case report: Chloroquine retinopathy. Thammasart Thai J Ophthalmol 2007;2:1-6.
13. Mawhibah Mohammed AA, Mohammed Ali QA. The role of clinical pharmacists in reducing adverse drug reactions. Int J Med Dev Ctries 2020;4:236-9.
14. Tangtavorn N, Yospaiboon Y, Ratanapakorn T, Sinawat S, Sanguansak T, Bhoomibunchoo C, *et al*. Incidence of and risk factors for chloroquine and hydroxychloroquine retinopathy in Thai rheumatologic patients. Clin Ophthalmol 2016;10:2179-85.
15. Rujiwetpongstorn J. Incidence and factors associated with chloroquine maculopathy in patients treated at Lamphun Hospital. Lanna Public Health J 2015;11:39-45.