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Ocular Toxicity of Chloroquin in Pakistani Patients

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INTRODUCTION

Aminoquinelone antimalarial drugs are quinine derivatives from bark of evergreen cinchona. They have been used before World War II for Rheumatoid Arthritis & since 1950's is Systemic Lupus Erythematosis[1]. Both of these drugs are well absorbed from the intestines. They are metabolized in liver and partially excreted by the kidney. They are widely distributed in all the tissues of the body[2]. They hydroxychloroquine does not cross the blood retinal barrier but chloroquin[3]. The frequency of occurrence of retinopathy varies from 0.001% to 40% according to the different published data[4]. Ocular toxicity results from the deposition of drug in structures of the eye including cornea, iris, ciliary body and retina[5]. The most serious complication results from retinal deposits which cause oxidative damage to the photoreceptors resulting in loss of colour vision especially red vision and severe retinal degeneration with loss of vision.

In Pakistan chloroquin is a widely prescribed medication for Rheumatoid Arthritis & Systemic Lupus Erythematosis and majority of these patients are not being monitored routinely for its toxicity and so far no study has been reported on this aspect.

Aims and objectives

The present investigation was done to establish the incidence of chloroquin induced ocular ocular toxicity in patients with Rheumatoid Arthritis, Systemic Lupus Erythematosis and other collagenopathies receiving long term chloroquin treatment.

PATIENTS AND METHODS

This is a prospective study conducted on patients visiting out patient Rheumatology Clinic at National Hospital and Medical Centre, Lahore from 1996-2000. Only those patients with active SLE or RA were included in the study who were taking chloroquin and who received regular eye examination including examination of visual fields, colour vision, slit lamp examination and fundoscopy. All of these patients had base line eye examination and subsequently repeat eye examinations were carried out every 3 months by qualified opthalmologists. Patients who were already taking chloroquin were included in the study only if their base line eye examination was normal.

Statistical analysis

Numerical data are reported as Mean±SD. Group comparison between cases and controls on these parameters was done using independent sample t-test. Chi-square test was used for analyzing differences in categorical variables A p value ≤ 0.05 was considered significant for all analyses.

RESULTS

This prospective study reports experience with 100 patients. The original study sample constituted 137 patients. However, complete follow up was only possible for 100. Thirty-seen patients did not complete the study either due to early drop out, failure to maintain follow up or refusal by the patient to take the medication as prescribed due to other side effects. Ocular toxicity was seen in 9 patients. Characteristics of patients with retinal toxicity are presented in Table 1. In table 2 comparisons of these patients with controls that did not manifest any ocular toxicity is presented.

The statistical analysis presented in Table 2 shows that both the causes with toxicity and controls without toxicity were comparable in terms of all the parameters evaluated.

It is interesting to note that controls that did not have any toxicity were, in fact, receiving higher mg/kg dose as compared to the cases although the difference between the two groups was not statistically significant. However, the mean total dose given to the controls was slightly less than that of the cases. The study did not attempt to look into the possible causes of this peculiar observation.

Table 1: Characteristics of individual patients with ocular toxicity.

Patient No	Diagnosis	Age (Years)	Weight (Kg)	Duration of Treatment	Eye Changes
1	SLE	36	62	5 months	Maculopathy
2	RA	55	75	2 years	Corneal deposit
3	RA	33	75	4 months	Absent foveal reflex Bilateral Macular Changes
4	RA	53	104	11/2 years	Corneal deposit
5	RA	37	72	6 months	Macular changes
6	RA	21	55	1 year	Bilateral Maculopathy
7	SLE	45	70	4 years	Corneal deposits
8	RA	68	65	4 years	Macular Changes
9	RA	50	60	3 years	Macular Changes

Table 2: Characteristics of cases vs controls.

Parameters	Cases (n=9)	Controls (n=91)	P values
Age in years	44.22±14.04	38.32 ±12.85	> 0.05*
Duration of treatment (Months)	22.33±17.80	21.36±19.43	> 0.05*
Daily dose (mg)	200 mg	200 mg	> 0.05*
Weight in Kg	70.89±14.22	62.68±13.87	> 0.05*
mg/kg dose	2.90±0.49	3.35±0.81	> 0.05*
Total dose administered (gms)	134±106.8	128.1±116.5	> 0.05*
Diagnostic categories			
Rheumatoid Arthritis	7	72	> 0.05**
Systemic Lupus Erythematosis	2	16	> 0.05**
JCA	0	3	> 0.05**

*, based on independent sample t-test
** based on Chi-square test

DISCUSSION

Aminoquinolones, notably chloroquin and hydroxychloroquin, are amongst the most commonly used disease modifying agents prescribed in patients suffering from a variety of connective tissue diseases[2]. Ocular toxicity is a serious side effect of these medications. This may manifest as corneal deposits or retinopathy, the later is further divided into (i), premaculopathy when the patient has either pigment changes or subclinical visual loss to red light only and (ii), maculopathy which presents as scotoma or loss in visual acuity. Premaculopathy is reversible on discontinuation of therapy but advanced macular disease characterized by Bulls eye lesion, optic atrophy, or diffuse pigmentation are irreversible and can even lead to loss of vision[6]. Patients who develop ocular toxicity may be entirely asymptomatic and thus regular eye examination by ophthalmologist during the course of treatment is mandatory especially to detect early cases without irreversible changes when full recovery is possible.

In Pakistan Chloroquin is extensively used, as hydroxychloroquin is not widely available and also is more costly than chloroquin. This study was carried out to evaluate the incidence of ocular toxicity in patients on long term chloroquin treatment for a variety of connective tissue diseases. Patients receiving chloroquin were prospectively followed in a Rheumatology Clinic with regular eye examinations by an experienced ophthalmologist at 3 month intervals for up to the time when ocular toxicity was detected when the drug was withdrawn. Patients without toxicity continued to receive the drug with periodic examinations as outlined. The median duration of chloroquin usage in the control group was 18 months. 59% of patients had been on chloroquin for 2 years where as 5.5% of patients in control group received chloroquin for over 7 years. This is different from the study reported by Puavilai et al who have reported a median duration of 2½ years of drug use with ocular toxicity in 23% of their cases. 9% had corneal deposits and 14.2% had Retinopathy[7].

In the present study chloroquin toxicity was

seen in 9% patients. This is considerably less than the 23% figure reported by puavilai et al. However, the mg/kg dose of chloroquin in the later study was not specified as the data on body weight of their patients was not available. Toxicity in our series occurred at a mean dose of up to 4.0 mg/kg/day. The toxicity was not related to duration of treatment and cumulative dose.

CONCLUSION & RECOMMENDATIONS

1. Ocular toxicity occurs in a significant number of patients on chloroquin and is not related to duration of treatment or cumulative dose.
2. Patients treated with chloroquin should be monitored for ocular toxicity by serial ophthalmological examination every 3 months.
3. Doses in excess of 4mg/kg/day are not recommended.
4. The authors propose a large prospective study to establish the true incidence of chloroquin induced ocular toxicity as weli to determine the safe maximum daily dose.

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