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Original Article

Magnitude of chlorpromazine induced ocular toxicity among psychiatric patients at Melik and Amanuel Hospitals

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Abstract

Background: *Chlorpromazine (CPZ), a typical anti-psychotic drug, has been associated with irreversible ocular toxicity signs which are dependent on total dosage and duration where exact values varied in different studies. In Ethiopia, there is no data on chlorpromazine induced ocular toxicity.The current study aimed to determine the prevalence of Chlorpromazine induced ocular toxicity.*

Method: *All consecutive psychiatric patients taking Chlorpromazine at a dose of 100mg/d or more for more than one month were included. Then, socio-demographic data, daily dosage and duration of Chlorpromazine treatment were obtained from self-administered questionnaire as well as patients' chart review. Visual acuity of each eye was taken using Snellen's illiterate "E" chart at a distance of 6 meters. Examination was especially directed to the lids and conjunctiva for pigmentation. Complete slit lamp examination was done to look for anterior segment toxicity signs and direct ophthalmoscope for posterior segment findings.*

Result*: Out of the total 92 patients examined, 30 (32.6%) (95% CI: 22-41.8) had signs of ocular toxicity ie 8 with rosette pigments, 11 with anterior stellate cataract alone and 11 with concomitant anterior stellate cataract and corneal changes. The minimum cumulative total dose resulting in ocular toxicity was in the range between 500gm and 750gm taken more than 5 years. ALL patients having anterior stellate cataract with corneal changes had severe visual impairment.*

Conclusion: *Chlorpromazine is associated with lens and corneal toxicity at a minimum cumulative dose ranging between 500gm and 750gm taken more than 5 years. Patients with concomitant lens and corneal changes had severe visual impairment. Close and combined management of patients on Chlorpromazine between ophthalmologists and psychiatrists is recommended.*

Keywords: Chlorpromazine, Ocular toxicity, Menilik Hospital

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Introduction

Chlorpromazine (CPZ, Largactil), introduced in 1953 has been widely used in general medicine and psychiatric diseases, especially in the long term intensive therapy of schizophrenic patients. Its pharmacological properties include competitive blockage of dopamine receptor **(1).**

This drug has anticholinergic properties leading to systemic and ocular adverse effects. Ocular structures most affected are sun exposed areas such as the eyelids and conjunctiva manifesting as a purplish discolorations and pigment deposits on the cornea and lens which was first described by Greiner and berry **(2).** These changes appear after long term use due to its photosensitizing properties **(3).**

Since then, studies have shown that the incidence of ocular toxicity signs varies from 22-80 % **(4-7).**The total cumulative dosage of chlorpromazine needed for inducing toxicity signs varies in different studies betwen100g-1000 g **(8-11).** Low visual acuity associated with such ocular changes and its irreversible nature has been described **(12, 13).**

However, there has not been much interest in the recent past, possibly due to decreased use in developed countries. Also, literature in this area from developing countries is scares. As there is reappearance in use of atypical antipsychotics, it is important for clinicians to be aware of these side effects, especially in developing countries since many patients are on typical antipsychotics due to its low cost.

The magnitude of chlorpromazine-induced adnexal and ocular toxicity is unknown in Ethiopia. The aim of this study is to see the magnitude of Chlor-

promazine induced adnexal and ocular side effects and assess the minimum total cumulative dose and the minimum duration required for ocular toxicity to occur.

Subject and methods

This is a hospital based cross-sectional study conducted at Amanuel and Menelik II referral hospitals over a period of one year (July 2016-July 2017). Ammanuel and Menelik hospitals are tertiary centers in Addis Ababa for psychiatry and eye care respectively. All consecutive patients attending the psychiatry clinics of both hospitals during the study period were the source population. Psychiatric patients taking Chlorpromazine at a dose of 100mg/d or more for at least one month at the two hospitals were included. Cases that refused to be part of the study or aggressive to examine were excluded. Patients with ocular diseases which tend to decrease vision and history of trauma to the eye were also excluded.

The principal investigator identified and obtained informed (verbal) consent from patients who were taking Chlorpromazine. Then, socio-demographic data, daily dosage and duration of Chlorpromazine treatment were obtained from self-administered questionnaire as well as patients' chart review. Visual acuity of each eye was taken using Snellen's illiterate "E" chart at a distance of 6 meters. Examination was especially directed to the lids and conjunctiva for pigmentation. Complete slit lamp examination was done to look for anterior segment toxicity signs and direct ophthalmoscope for posterior segment findings.

The following operational definitions were used to evaluate the ocular toxicity of Chlorpromazine **(14)**

Eye lid toxicity:- a purplish discoloration of the lid skin

Conjunctival toxicity:- a hyper-pigmented triangle whose base is towards the limbus in the interpalpebral zone.

Corneal toxicity:- golden brown discrete deposits diffusely distributed in the epithelium, stroma or endothelium of the cornea.

Lens toxicity

Grade 1:- discrete golden brown deposits in the anterior pole of the lens.

Grade 2:- a star shaped gold brown deposits in the anterior surface of the lens (rosette opacity).

Grade 3:- dense whitish granular anterior opacity (stellate cataract)

Cumulative dose of Chlorpromazine: – dose of Chlorpromazine that has been used during the treatment period.

The collected questionnaire was checked manually for its completeness and entered in to SPSS version 20 by two data entry clerks. The collected data was entered in to and analyzed by statistical package for social science version 20. Descriptive statistics was used to describe data by using mean, frequency, percent and standard deviation. Moreover inferential statistics was used for testing association of ocular toxicity with the dose and duration of Chlorpromazine by using chi-square test and $P \leq 0.05$ was considered statistically significant.

Results

A total of 92 patients on chlorpromazine were examined. There were 62/92 (67.4%) males and 30/92 (32.6%) females as seen in **table 1**.

Table 1- Socio-demographic characteristics of patients on Chlorpromazine

Variables	Total patients	Ocular toxicity/ group (%)	Relative Risk
Sex			
Female	30	8 (26.7%)	1.0
Male	62	22 (35.5%)	1.3
Age			
<30	32	7(21.9)	1.0
>30	60	23(38.3)	1.8
Occupation			
Jobless	47	15 (31.9%)	1.1
Farmer	10	3 (30.0%)	1.0
Housewife	10	3 (30.0%)	1.0
Others*	25	9 (36.0%)	1.2

*private and government employees, students

The mean age was 36.6 (±-9.4SD) years, the range being from 16 years to 56 years. Majority of the participants 47(51.1%) were jobless. The total cumulative dosage of Chlorpromazine taken by our patients varied between 3g and 3240g. The duration that our patients took Chlorpromazine ranges from 1 month to 25 years**.**

The prevalence of Chlorpromazine induced ocular toxicity was 32.6% (95% CI: 22-41.8).The association of ocular toxicity with clinical variables like age (p=0.109), sex (p=0.398) and occupation (p=0.977) was considered but no association was found. However, the total dose and the duration of maximal dose were highly significantly associated with Chlorpromazine ocular toxicity (P=0.000).

Only 3 (3.3%) of the total patients examined had history of eye glass use and 2 of them had occasional use and had the ocular toxicity signs. The remaining one patient had a full time wear and was on Chlorpromazine at a cumulative dose in a range of 500-750g for more than 10 years but had no ocular toxicity signs.

Of the 92 patients examined, lens changes were seen in 30 (32.6%) of the cases. Eight of 30 (26.7%) patients had a grade 2 toxicity which was star shaped

lens pigmentation. The minimum total cumulative dose of chlorpromazine resulting in Lens star pigmentation was between 500-750g (**table 2)** and the minimum duration was between 5-10 years **(table 3).**

Table 2: Lenticular changes associated with cumulative total dosage of Chlorpromazine (n=92).

Total dosage of Chlorpromazine (grams)	Number of patients	Lens changes (%)	Relative Risk
0-250	35	0(0)	0
251-500	22	0(0)	0
501-750	14	10(71.4 %)	71.4
>750	21	20 (95.2)	95.2

Table 3: Lenticular changes associated with duration of Chlorpromazine intake

Total duration (years)	Number of patients	Lens changes (%)	Relative Risk
≤5	15	0	0
6-10	34	3 (8.8)	8.8
11-15	23	8 (34.7)	34.7
≥16	20	19 (95.0)	95.0

There was a significant association between lens changes and dose and duration of Chlorpromazine intake (p=0.00). All patients with this type of lenticular change alone had normal visual acuity. Only three of them complained of photophobia.

Twenty two 22/30 (73.3%) had grade 3 toxicity manifested with anterior stellate opacity. The minimum total cumulative dose of chlorpromazine resulting in stellate opacity of the lens was in the range of 500-750g and the minimum duration was 5-10 years. But, 95% of lens changes occurred at a dose above 750g taken more than 16 years.

Corneal changes were seen in 11 of 92 (12.0%) patients evaluated. All cases with corneal findings had also concomitant lenticular changes suggesting that lens changes precede corneal changes. These patients (n=11**)** had diffuse corneal pigmentation which was associated with grade three lens findings in this study. The minimum cumulative total dose of chlorpromazine resulting in corneal pigmentation was between 500-750g **(table 4)** and the minimum duration was between 10-15 years **(table 5).**

Table 4: Corneal changes associated with cumulative total dosage of Chlorpromazine (n=92).

Total dosage of Chlorpromazine (grams)	Number of patients	Corneal changes (%)	Relative Risk
0-250	35	0(0)	0
251-500	22	0(0)	0
501-750	14	2(14.3 %)	14.3
>750	21	9(42.9%)	42.9

Table 5: Corneal changes associated with duration of Chlorpromazine intake

Total duration (years)	Number of patients	Corneal changes (%)	Relative Risk
≤5yr	15	0	0
6-10yr	34	0	0
11-15	23	1 (4.3%)	4.3
≥16yrs	20	10 (50.0%)	50.0

There was a significant association between corneal findings and dose as well as duration of Chlorpromazine intake (p=0.00).

From the total 30 individuals with signs of ocular toxicity, 8 (26.7%) had normal visual acuity while 22 (73.3%) had visual impairment. All the patients with corneal findings (n=11) had visual complaints, 8/11 (72.7%) had blurring of vision and 3/11 (27.3%) had photophobia. The fact that all patients with corneal signs had concomitant lens signs resulted in severe visual impairment of these patients on visual acuity testing **(table 6).**

Table 6: Visual acuity of patients with Chlorpromazine ocular toxicity sign

Visual acuity	WHO category	Sign of ocular toxicity	Number of eyes
6/6-6/12	Normal	Rosette pigment	8(26.6%)
≤6/18-6/60	Moderate impairment	Anterior stellate cataract	11(36.7%)
<6/60-3/60	Severe impairment	Anterior stellate and corneal pigments	11(36.7%)

Discussion

The prevalence of Chlorpromazine induced ocular toxicity in this study was found to be 32.6% (95% CI: 22-41.8). Munde T et al has found the prevalence of ocular side effects for antipsychotic drugs to be 18.0% **(13).** The higher prevalence might be due to difference in study subject compositions and sun exposure due to geographic location. No obvious abnormalities were noted on external examination and no fundus changes were seen which could be attributed to Chlorpromazine.

Kinross et al have described macular pigmentation with other phenothiazine family mainly Thiorazidine and Piperidine **(15).** The fact that our patients were mostly on Chlorpromazine would explain this finding. The absence of skin pigmentation could be explained by racial differences. In addition, skin changes are said to be present only in patients with impaired glucuronide conjugation of Chlorpromazine and its metabolites.

Lens changes were the commonest (32.6%) ocular toxicity of Chlorpromazine followed by a combination of lens and corneal changes which were seen in 12.2%. Corneal changes alone were not seen which suggests that the lens changes preceded corneal changes. This goes with Barsa et al who reported lenticular changes in 27% of the cases and combined lenticular and corneal changes in 5% only **(11)**. Delong has shown that 37.0% of the cases had lens changes and 18% had corneal changes **(16).**

Malthon also found lens changes in 36.0% and corneal changes in 17.0% of the patients. On the other hand, a study done by Siddall reported lenticular involvement in 78.0% of cases **(10)**. Because of the site of the lesions in the anterior part of the lens and posterior cornea, either the drug or its metabolite in the anterior chamber might be responsible for these ocular signs. In addition, since these are exposed structures of the eye, photosensitivity may also play a role.

The minimum total cumulative dose of Chlorpromazine resulting in ocular toxicity in this study varied from 500gm to 750gm. Alexander et al found a total cumulative dose of 324gm taken for 2 years or over 2gm per/month to produce ocular toxicity while Crane et al reported that the minimum cumulative quantity of Chlorpromazine sufficient to produce eye manifestation varied from 100gm to 600 gm **(2, 17)**.

On the other hand, Buffaloe with his associates and Wetterholm et al have placed the critical cumulative dose value of Chlorpromazine at 1000g taken for a minimum duration of 5 years to produce ocular toxicity **(3, 5).** The possible explanation for this variation may be differences in metabolism, combination of other antipsychotic drugs which may have a protective effect, genetic susceptibility and sun glass use.

Half of the patients with anterior stellate cataract and

corneal changes had severe visual impairment comparable with a Spanish study which found cataract in 40.0% of cases and reduced visual acuity in 26.0% of their patients **(18).** This visual reduction is due to its effect on both the cornea and the lens.

The strength of our study is that all patients on Chlorpromazine were included without limiting dose and duration to get the minimum range of dosage and duration leading to toxicity. One of the limitations of this study was the difficulty to obtain the exact cumulative dosage and duration of Chlorpromazine for referred patients due to incomplete data. Some patients were also thought to discontinue the drug during symptom free periods for unspecified period of time while some take overdose for suicidal purposes. Some patients were kept on more than one drug which made it difficult to control its toxic effect on the eye.

In conclusion, Chlorpromazine is associated with lens and corneal toxicity at a minimum cumulative dose ranging between 500-750g taken for more than 5 years. Patients with both lens and corneal changes together had severe visual impairment. Close and combined management of patients on Chlorpromazine between ophthalmologists and psychiatrists is recommended.

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