Chlorpromazine is a low-potency neuroleptic used in the treatment of various psychiatric disorders. Chlorpromazine-induced cataract and corneal pigmentation was first described by Greiner & Berry in 1964. The prevalence in patients treated over time with large doses of CPZ therapy, ranges from 15% to 74%. Though other low-potency neuroleptics like thioridazine and fluphenazine have been reported to cause pigmentary changes, characteristic corneal and lenticular pigmentation is predominantly if not exclusively a side-effect of CPZ. We report a case of a 45-year-old female with ocular effects due to long-term CPZ therapy for bipolar disease.

Case report

A 45-year-old female had been taking treatment for manic-depressive psychosis with chlorpromazine 300 mg per day for 25 years. In addition, she was found to have received lithium 300 mg and haloperidol 5 mg, both twice daily for florid psychotic symptoms. She came with a complaint of hazy vision of 9 months duration. On examination she had a visual acuity of 6/36 in both eyes. Penlight examination revealed a clear cornea with opacity in the center of the lens in both eyes. Slit-lamp examination revealed pigment dusting over the back of the cornea, which was diffuse, granular, and brown in color; most prominent at the level of deep stroma and endothelium. There was a star-shaped anterior polar cataract, which was golden brown in color involving the anterior capsule and subcapsular epithelium, characterizing Grade IV lenticular pigmentation (Figure 1). The rest of the lens was clear. The distribution was symmetrical in both eyes. Two independent clinicians documented the condition. The pupils were dilated with 1% tropicamide for retinoscopy. A dilatation of only 4 mm could be achieved. Fundus examination by indirect ophthalmoscopy was normal. Systemic examination was normal; apart from a few extrapyramidal symptoms there were no other side-effects of CPZ, including skin discoloration. Investigations including liver function tests and peripheral smear were normal. With subjective correction, the patient’s vision improved to 6/6. With the psychiatrist’s consultation, CPZ was substituted with trifluoperazine.

Discussion

Chlorpromazine is an aliphatic phenothiazine used in all types of psychosis, especially schizophrenia. The adverse effects include drowsiness, lethargy, postural hypotension, anticholinergic side-effects, infertility and extrapyramidal symptoms, which are dose-related. The hypersensitivity reactions are cholestatic jaundice, skin rashes, photosensitivity and agranulocytosis. Blue pigmentation of exposed skin, corneal and lenticular opacities and retinal degeneration occur rarely after long-term use of high doses of phenothiazines. The most prevalent ocular side-effect associated with CPZ therapy is anterior capsular and subcapsular lens pigmentation, followed by corneal endothelial pigmentary changes. Alexander and associates found 67% of a group of patients to have the former, while 45% exhibited the latter. However, both conditions rarely reduce visual acuity, and patients may occasionally report glare and halos around lights. Thaler and associates described lenticular pigmentation as occurring in 5 stages. They range from isolated, brownish, dust-like specks in the anterior surface of the lens to stellate cataracts that can impair visual acuity. The stellate pattern, which characterizes Grade IV lenticular changes, has a dense central area with radiating branches as seen in our patient. The lens changes at this stage can be recognized with a penlight, and diagnosis does not necessarily require slit-lamp examination.

Corneal pigmeny changes almost invariably occur in patients who have concomitant lens opacities in the higher grades. The pigmentation is white, yellow-white, brown, or black and occurs at the level of the endothelium and Descemet’s membrane, primarily in the interpalebral area and may also occur in the epithelial layer. There is often little or no corneal involvement with lens opacities Grades I and II, but Grades III and higher have detectable corneal pigmentation ranging from light to heavy. In severe cases it can affect the deep stroma.

Figure 1: Stellate cataract caused by chlorpromazine therapy.
The reported frequency of lenticular opacities is influenced by the nature of the population and by the examining ophthalmologist’s familiarity with the entity. These changes occur with low-potency neuroleptics such as CPZ or thioridazine and are dose-related. Lenticular pigmentation is rarely evident when the total cumulative dosage is less than 500 g, and the prevalence of pigmentary changes increases with total dosage between 1000 and 2000 g. Since some psychiatric conditions may require daily dosages exceeding 800 mg, lenticular pigmentation can appear in as early as 14 to 20 months of therapy. Dosages consisting of 2000 mg daily have caused lenticular changes in as early as 6 months of therapy.

Lithium is known to increase extrapyramidal symptoms, increase risk of derelium and malignant neuroleptic syndrome when combined with CPZ though there is no documented evidence of increasing its ocular side-effects. The other ocular changes that can occur with CPZ toxicity are discoloration of the conjunctiva, sclera, skin of the lids and pigmentary changes in fundus, which were not noted in this patient. Poor mydriasis noted in this patient is probably due to the infiltration of the dilator pupillae muscle of the iris by pigments.

Chlorpromazine deposition in high levels can cause decreased visual acuity and significant skin discoloration. Surprisingly, in our patient, though the cumulative total dose exceeded 2500 g, there was no skin discoloration. It is suggested that only individuals with impaired glucuronide conjugation of CPZ and its metabolites are susceptible to skin changes. Another postulation could be the protective effect of haloperidol though the exact mechanism is unknown. Furthermore, photosensitivity of the skin to the sun without increase in skin pigmentation is much more common and has a significant relationship with eye changes rather than skin pigmentation.

The precise nature of the pigmented granules in the cornea and lens is unknown. The pigmentary changes may be a result of drug interaction with ultraviolet light as it passes through the cornea and lens, causing exposed proteins to de-nature, opacify, and accumulate in the anterior subcapsular region of the lens as well as in corneal stroma. There is a general agreement that the pigment deposited is melanin, probably combined with the neuroleptic or one of its metabolites. Usually, the corneal and lenticular pigmentary changes progress to a point beyond which no further changes are observed. On reduction or discontinuation of drug therapy, the pigmentary deposits are generally irreversible though some reports of reversible epithelial keratopathy have been noted. This may be because the deposits associated with CPZ therapy are located in avascular tissues. In rare instances the lenticular pigmentation can begin after CPZ therapy is discontinued.

The differential diagnosis includes axial punctate opacities that are found in about 10% of all normal individuals over the age of 40. We believe that individual factors like drug metabolism may play a role in susceptibility to corneal and lenticular opacities.

Patients receiving high-dosage or long-term, low-dosage CPZ therapy should be monitored annually by careful slit-lamp examination. Since lens pigmentation is the most frequent ocular change observed, slit-lamp examination of the lens with the pupil dilated is the most direct method for detecting early CPZ toxicity. It is believed that the ocular changes do not occur with higher potency neuroleptics such as haloperidol and trifluoperazine. Though the ocular changes do not reverse even when CPZ is withdrawn, the institution of high-potency neuroleptics would at least arrest the progress of the opacities. The use of spectacle lenses, presumably to reduce the amount of ultraviolet light entering the eye, has been unsuccessful in reducing the prevalence of ocular toxicity. The use of d-penicillamine has also not been found to be successful in reversing the ocular pigmentary changes associated with long-term CPZ therapy.

If corneal and lens changes occur but visual acuity is not affected and the patient is asymptomatic, the drug dosage can be continued without modification. If the patient becomes symptomatic, the dosage should be reduced or therapy should be changed to a different drug.

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**References**


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