Principles and Practice of Clinical Electrophysiology of Vision

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Retinal Toxicity From Thioridazine and Other Phenothiazines

Michael F. Marmor

The potential of phenothiazines to cause retinal toxicity was recognized in 1956 when pigmentary retinopathy was described in patients receiving the experimental phenothiazine NP207.[14, 20, 43] This drug was promptly withdrawn from human usage, but within 4 years similar cases were observed with thioridazine (Mellaril).[44] Both of these drugs have a piperidylethyl side chain (Fig 78–1), a feature lacking in other phenothiazines except for mesoridazine (Serentil), which is a metabolite of thioridazine. There is little evidence that significant retinal damage has occurred from any phenothiazines other than thioridazine and NP207, so it is preferable to use more specific terms such as thioridazine retinopathy.

THIORIDAZINE AND NP207

Clinical Findings

The development of thioridazine retinopathy depends most critically on the daily dose of the drug rather than on the cumulative amount as appears most relevant for chloroquine toxicity. Symptoms of blurred vision or poor dark adaptation can develop within a few weeks of high-dosage administration (e.g., 1,200 or 1,600 mg/day),[9, 10, 34, 44, 46] and only very rare cases of retinopathy have been reported with dosages at or below 800 mg/day, which is generally accepted as the upper allowable limit.[1, 16, 22] There have also been rare cases that implicate toxicity from long-term usage,[1, 22] but this is clearly an uncommon event if it occurs.

New cases of thioridazine retinopathy are infrequent nowadays since the psychiatric profession is generally aware of the retinopathic risks and the acceptable dose level. As early as 1961 the *Physicians' Desk Reference* noted pigmentary retinopathy as a side effect at "high doses,"[33] and the maximum recommended dose has long been listed as 800 mg. Retinopathy sometimes develops when a patient (or sadly a doctor) tries to improve the therapeutic effect by multiplying the daily dose. A recent report notes that blood levels of thioridazine may be elevated severalfold by the simultaneous administration of propranolol[41]; this could potentially bring safe doses into a toxic range.

The fundus changes in thioridazine retinopathy are striking and very characteristic. In the acute stage of toxicity (Fig 78–2, Plate 10), one sees coarse, brownish pigmentary stippling in the macula and posterior fundus.[10] Even though treatment with the drug may be stopped, these pigmentary changes will evolve over time to produce a quite different (but equally characteristic) appearance of patchy or nummular retinopathy (Fig 78–3, Plate 11) with geographical areas of atrophy and hyperpigmentation.[21, 28] This evolution of fundus appearance has led to some confusion about whether the retinopathy progresses after cessation of the drug therapy. If

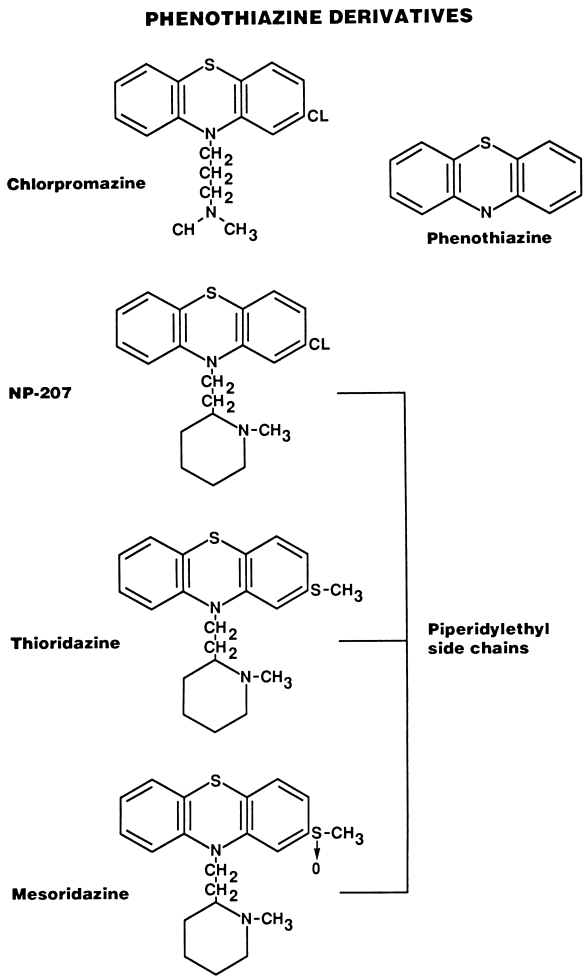

FIG 78–1.
Chemical structure of some phenothiazines.

visual symptoms are recognized promptly and treatment with the drug stopped, a degree of functional recovery can occur,[8, 9, 24] although pigmentation will persist and evolve. After large and prolonged doses, retinal damage is irreversible; there is minimal if any recovery after cessation of drug therapy, and there may be late deterioration.

There is no specific treatment for thioridazine retinopathy other than cessation of drug usage. However, one might advise patients who have suffered thioridazine retinopathy to take routine steps to minimize light-induced or oxidative damage, which may contribute to retinal aging and compound the retinal damage.[25] For example, patients should avoid stressful light exposure (especially from short wavelengths) and a deficiency in antioxidant vitamins and minerals, steps that are probably prudent for any individual with compromised retinal function.

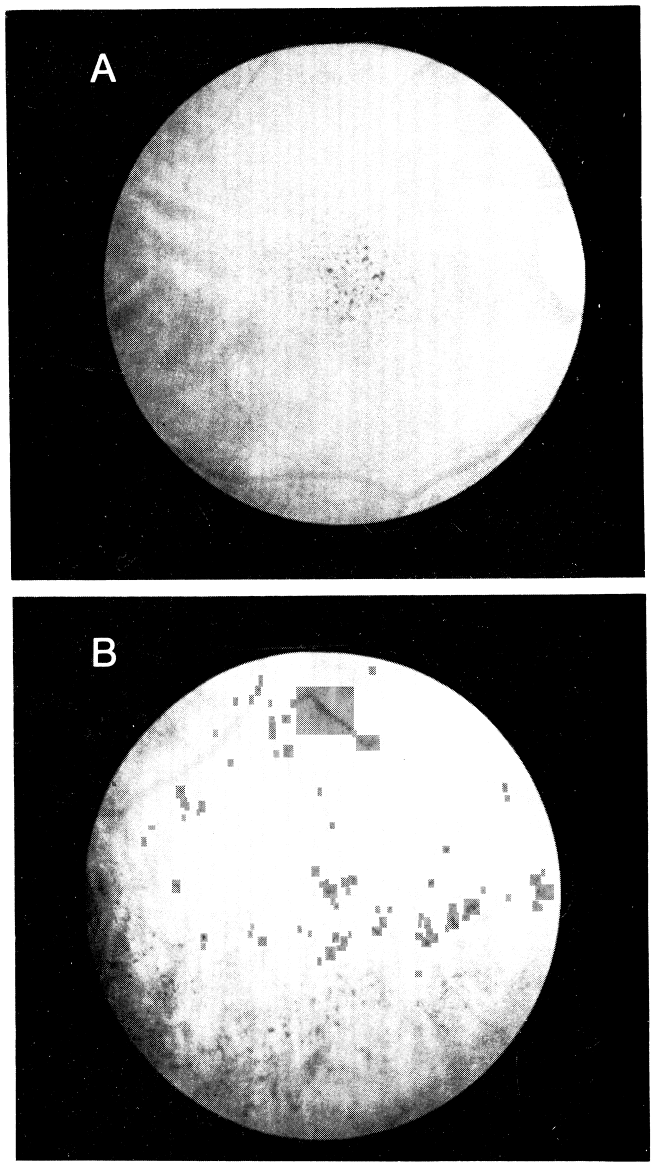

FIG 78–2.
Examples of early thioridazine retinopathy. Coarse granular pigmentation is present in the macula and beyond. **(See also Color Plate 10.)**

Stable vs. Progressive Retinopathy

The issue of whether there is late progression of retinopathy, as may occur after chloroquine toxicity,[12, 32, 37, 38] is important. The fundus picture in thioridazine toxicity unquestionably evolves, and a few reports document late visual loss or electrophysiological damage after thioridazine therapy has been stopped.[10, 13, 21, 28] However, the literature also documents the fact that visual function often improves during the first few months or year after stopping treatment with the drug,[8, 9, 24, 26] despite a progres-

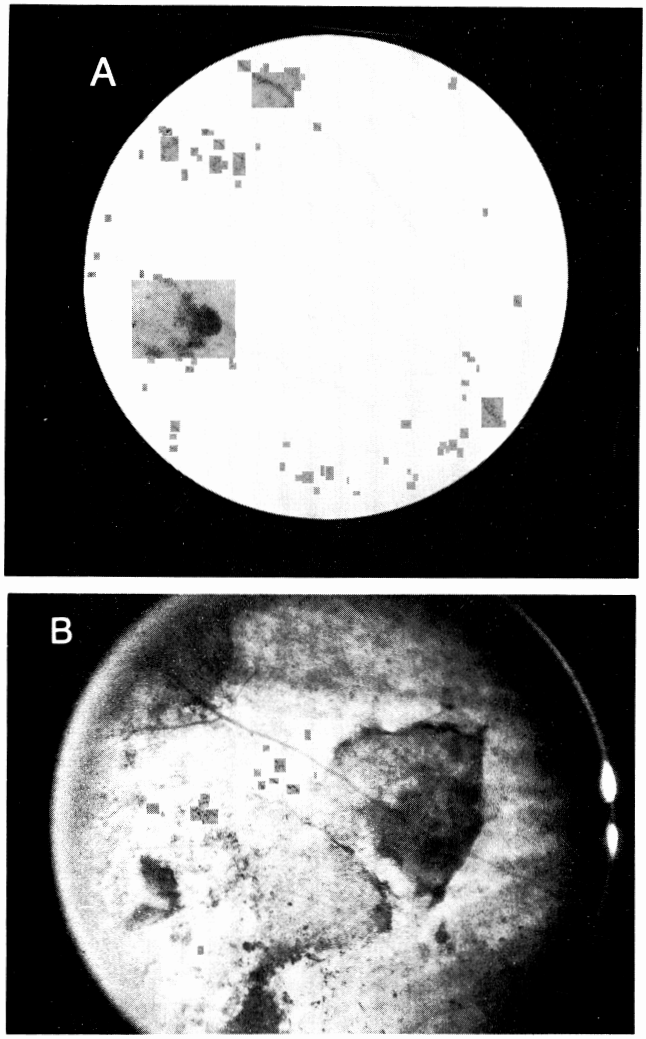

FIG 78–3.
Examples of late thioridazine retinopathy. The appearance has changed to a nummular pattern of atrophic and hyperpigmented patches. **(See also Color Plate 11.)**

sion of fundus lesions from grannular to nummular retinopathy. Thus, one must distinguish two phases of thioridazine retinopathy: in the first 1 to 2 years, there is evolution of chorioretinal scarring that is independent of visual function (which is typically stable or improving). After 1 to 2 years, there may be gradual expansion of nummular fundus lesions, and visual function either can be stable or can slowly deteriorate.

A question that cannot be definitively answered is whether this occasional late deterioration represents chemical toxicity by drug retained in the retinal pigment epithelium (RPE). This is possible, of course, but is a bit implausible after visual function had been improving or stable in preceding years. Expansion of chorioretinal scars may occur with aging (in macular degeneration) and in disorders where there is presumed subclinical damage to the RPE (postulated[31, 39] to explain the "creep" in macular photocoagulation scars). As a systemic drug, thioridazine damages the RPE diffusely, and the patchy nature of the retinopathy probably results from subtle regional differences in toxic effect; thus it would not be surprising for the patches to expand over time into the broader areas that were damaged at the time of drug ingestion without postulating a reservoir of continued pharmacological toxicity.[26] Regardless of its etiology, the occasional occurrence of late progression means that patients with thioridazine toxicity need to be followed with quantitative tests such as the ERG and visual fields. The use of functional tests is important because a progression of pigmentary damage is not necessarily equivalent to a progression of functional damage (as evidenced by the behavior of thioridazine retinopathy in the first 1 to 2 years).

Physiological Testing

Generally speaking, the electroretinogram (ERG) is depressed in proportion to the amount of visible damage to retina and pigment epithelium (Fig 78–4). In severe cases both the ERG and electrooculogram (EOG) are irreversibly extinguished. Few reports have attempted to differentiate the physiological parameters more precisely. Both cone and rod signals are depressed in severe cases[4, 8, 21, 28, 34]; Tamai and Holland suggested that scotopic testing may be more sensitive than photopic testing in mild cases.[42] There are no data on whether the EOG might be affected earlier or more specifically than the ERG, as might be expected if the damage were localized initially to the pigment epithelium. EOG results have ranged from normal[10] to an unrecordable light/dark ratio[28] and have generally correlated with the level of ERG damage. Miyata and colleagues[30] have reported that usage of thioridazine at ordinary (*not* retinopathic) doses selectively suppresses the oscillatory potentials, but the clinical significance of this observation is unknown. The macular ERG can also be reduced.[10] Visual evoked responses have not generally been recorded. Since the toxicity of the drug and the onset of symptoms are relatively acute, electrophysiology is used more often to document the extent of damage than to detect the earliest signs of damage (as is done for chloroquine and its analogues).

A review of the many published reports of thio-

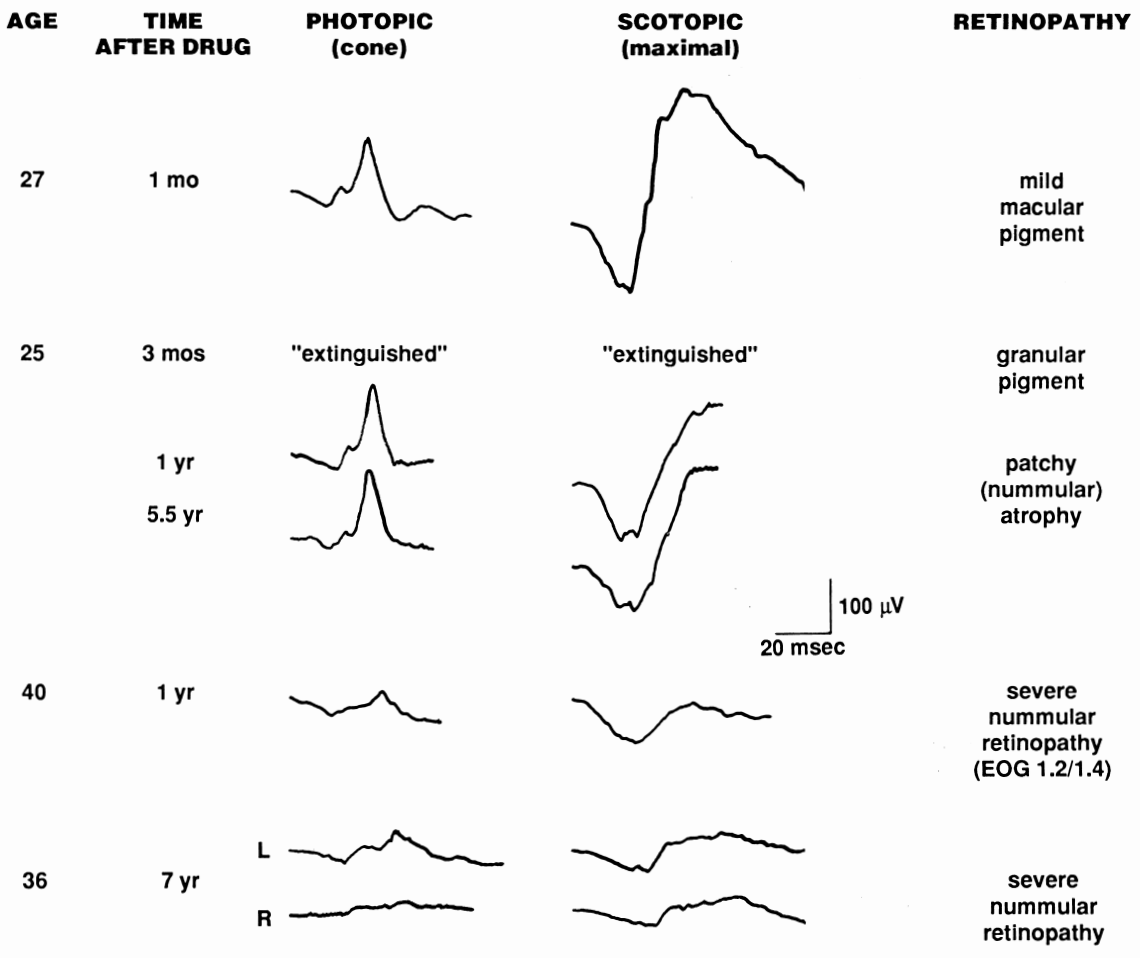

FIG 78–4.
Range of ERG findings in four cases of thioridazine retinopathy. The response is normal in patient 1 and nearly unrecordable in the right eye of patient 4. The ERG is roughly correlated with the severity of visible retinopathy. Note that patient 2 progressed from granular to nummular retinopathy, but the ERG improved from a very low signal (extinguished to a hand-held flash) to a relatively normal one (recorded with a full-field flash) that remained stable over 4½ years.

ridazine retinopathy (see the reference list) shows that abnormalities in visual acuity, visual field, contrast sensitivity, glare sensitivity, and dark adaptation (Figs 78–5 and 78–6) occur in accordance with the general degree of organic retinal damage that is present. Scotomas tend to match the areas of pigmentary and atrophy change and may spare only a tunnel of vision when damage is severe. Color vision testing may show tritanomalous errors typical of retinal disease, but the pattern of errors is often irregular. Contrast sensitivity is typically poor and may account for a variety of subjective complaints.

There may sometimes be difficulty in distinguishing organic symptoms from psychogenic overlay since many patients using this drug have significant psychiatric disease and some will amplify or deny symptoms. A patient of mine,[26] for example, had isolated scotomas in 1986 that coalesced to leave only 10 degrees of tunnel vision by 1988, at which time he began to use a long cane. However, fundus photographs and the ERG showed absolutely no change, and after considerable discussion and confrontation his vision "improved," and his fields returned to their baseline level. This patient unquestionably had retinal damage and visual field loss from thioridazine retinopathy, but erroneous conclusions about the nature and progression of his disease might have been drawn if objective testing had not been performed.

Mechanism of Toxicity

Histopathology of an eye with advanced thioridazine retinopathy showed disorganization of photore-

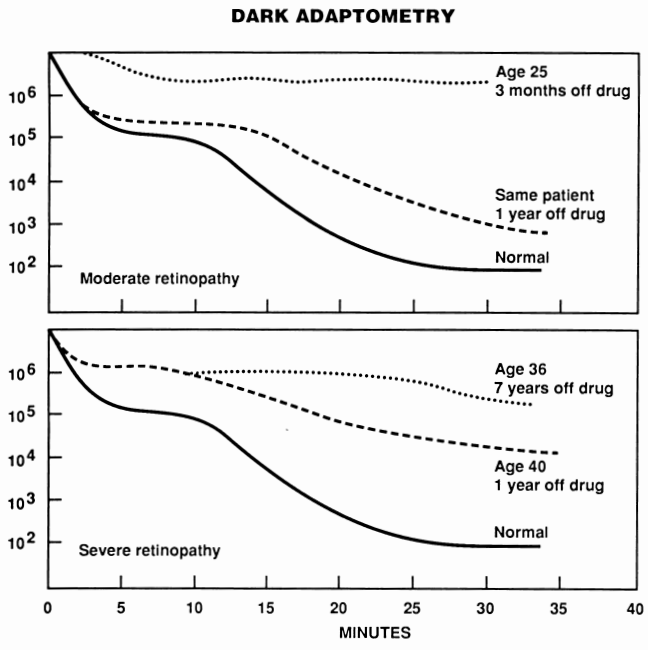

FIG 78–5.
Dark adaptometry in thioridazine retinopathy: same patients (identified by age) as in Figure 78–4. *Top*, improvement after cessation of thioridazine therapy; *bottom*, impaired dark adaptation in two other patients.

ceptor outer segments and a loss of underlying pigment epithelium and choriocapillaris.[29] The authors suggest that the photoreceptor damage may be the initial event since areas were noted where damaged photoreceptors overlay morphologically intact RPE. This is consistent with experimental NP207 toxicity in the cat, which involves the photoreceptors as the primary cell of injury.[15, 27] Nevertheless, the mechanism of cellular damage remains unknown. Thioridazine binds to melanin, but binding alone seems unlikely to be responsible for the toxicity since other phenothiazines bind similarly and are essentially nontoxic.[6, 35] Furthermore, thioridazine uptake has been documented in the retina as well as the choroid.[19]

Thioridazine inhibits succinic dehydrogenase and activates lactic dehydrogenase to a somewhat greater degree than do some other phenothiazines,[6, 27] but it is speculative whether this action accounts for the retinopathy. In vivo, moderate doses reduce the oscillatory potentials in rats,[7] but the reason for this selective effect or its relevance to toxic retinopathy is unknown. A report by Ivaneina et al.[17] suggests that toxicity is not related to lipid peroxidation.

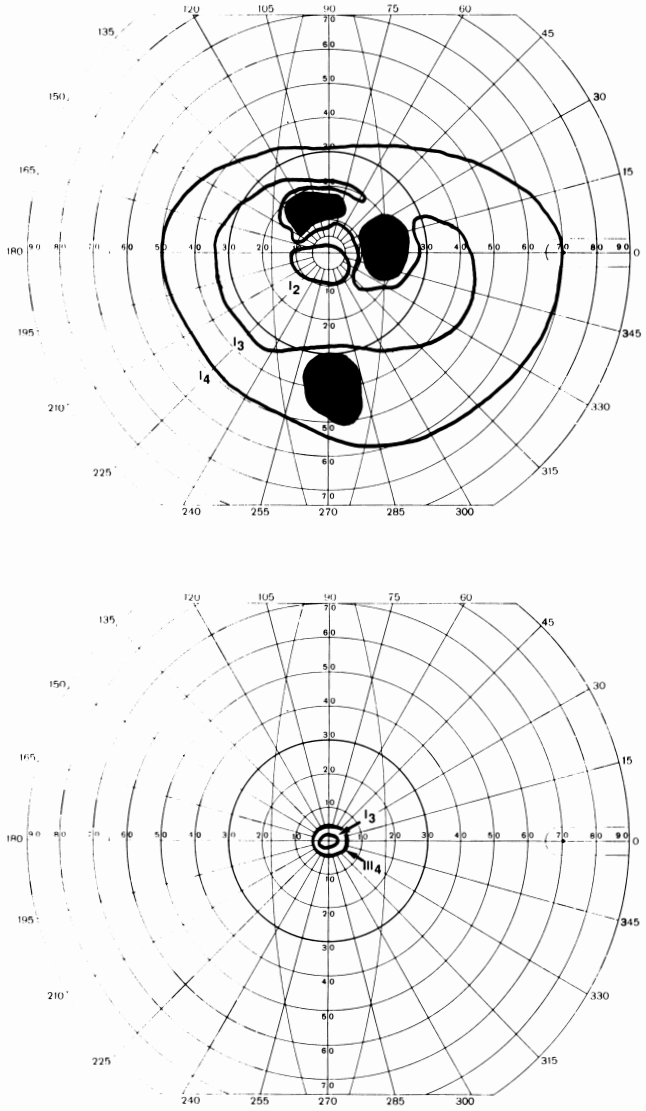

FIG 78–6.
Representative visual field changes in thioridazine retinopathy: same patients as in Figure 78–4. *Top*, the 25-year-old patient tested 2 years after stopping thioridazine therapy; *bottom*, the 36-year-old patient, 7 years after thioridazine treatment.

OTHER CLINICALLY USED PHENOTHIAZINES

Mesoridazine is a metabolite of thioridazine, has the same side chain, but has not been reported to cause retinopathy.[11] However, this drug is more potent psychologically and is given in roughly half the dosage, so a greater degree of abuse would be necessary to produce retinopathy.

There are reports of retinopathy after chlorproma-

zine (Thorazine), which is probably the most widely used phenothiazine agent.[2, 40] However, the definition of this chlorpromazine retinopathy is quite vague, and it is clearly *not* the type of severe well-demarcated pigmentary degeneration that is associated with thioridazine. For example, one author reported some cases with "fine clumping" of pigment after chronic ingestion of 2,400 mg chlorpromazine per day. In view of the fact that millions of individuals have taken this drug and that many have cumulative total doses in the kilograms, it seems highly significant that so few (if any) cases of functionally disabling retinopathy have been reported.[36] Some years ago I examined a number of patients who had heavy chlorpromazine deposition on the lens and cornea (a common finding in chronic users[45]), but none had visual acuity or field loss, pigmentary changes (that were distinguishable from age-related damage), or electrophysiological abnormalities. Reports of retinopathy with trifluperazine or other phenothiazines are of questionable clinical significance.

Although chlorpromazine retinopathy is not a clinical concern, chlorpromazine administration can produce electrophysiological changes in experimental animals. Chronic administration reduced the ERG in albino rats but seemed ineffective in pigmented animals.[23] In cats[3] and sheep,[5] the ERG a- and b-waves were diminished by acute administration, and the sheep c-wave developed oscillations after an initial decrease.[5] In rabbits, the ERG b-wave increased during intravenous infusion of chlorpromazine, and the effect was the same in pigmented vs. nonpigmented animals.[18]

SUMMARY

Thioridazine retinopathy remains a genuine risk as long as this drug is used clinically. Recognition of the findings in thioridazine toxicity is important so that the drug treatment can be stopped as early as possible and so that the retinal damage is not confused with other types of disease (such as retinitis pigmentosa). The retinopathic risk from other phenothiazines without piperidylethyl side chains is probably very low, and generalized "phenothiazine retinopathy" is not an entity of clinical significance. Electrophysiological evaluation in thioridazine retinopathy does not show any unique pattern of photoreceptor or RPE damage, but is important to document the degree of damage. Keep in mind that patients with thioridazine retinopathy often have psychiatric disease and that psychophysical test results may be modified by nonophthalmic factors. Periodic follow-up examinations are important since the fundus changes evolve over time and may or may not be associated with visual loss.

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