Drug toxicity and visual fields

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ABSTRACT — Many drugs used in the treatment of systemic pathologies may cause retinal or neurotoxic side effects which affect visual fields. This paper discusses the role of the drug history, personal health history, and testing procedures in evaluating these toxic visual fields. Specific drugs are cited which may cause toxic visual field defects.

KEY WORDS — visual fields, retinotoxic drugs, neurotoxic drugs, case history, color vision, visual acuity, color fields, baseline studies.

With the passage of legislation enabling optometrists to use diagnostic pharmaceutical agents, there has been increased emphasis on knowledge of pharmacology and pharmaceutical agents. The optometrist must understand the systemic and ocular actions of those diagnostic pharmaceutical agents, indications, and contraindications for their own use, interaction of those drugs with other pharmaceutical agents, and the side effects that may be associated with their use.

The introduction of therapeutic agents with greater efficacy has produced an increasing awareness of the toxicity of those agents and is now "considered the most critical aspect of modern therapeutics."[1] The nature of the toxic effects and their incidence are increasing with the introduction of new drugs.[2] This paper is intended to discuss those systemic therapeutic agents which have been shown to be clinically significant in producing retinotoxic and neurotoxic visual field changes.

The toxic effects of therapeutic agents can be manifested in many of the structures of the visual system.[3] Patients may present with many visual signs and symptoms. The practitioner must attempt to differentiate those which are due to ocular and systemic diseases from those which are due to toxic reactions.[4] This differentiation is a difficult one even under experimental conditions and poses a great challenge to the practitioner.[5] Visual field testing is an integral part of the clinical routine used to evaluate drug toxicities and there is an increasing need for their use.

Identification of those diseases which are drug induced requires knowledge of the various pathologies which may affect the visual system, those which may be due to drug toxicities and the specific drugs that could produce the observed pathologies.[6]

As the vision care specialist in the health care team, the optometrist must use all of his clinical knowledge and techniques in evaluating pathological conditions of the visual systems to attempt to differentiate those pathologies which are drug induced.

There are many drugs which are used to treat systemic diseases which will produce retinotoxic and optic nerve diseases. The clinical techniques which are useful in evaluating those effects are the case history, ophthalmoscopy, color vision testing, and visual fields.[7]

The case history must be complete and detailed and should include a description of any visual signs and symptoms in relationship to the current or past illnesses.

In many instances, the patients will not know the specific drug which they are taking. Knowledge of therapeutic agents used to treat specific diseases will alert the practitioner to the possibility that potentially toxic agents are being taken.

The drug history should include all prescription and over-the-counter medications the patient is currently taking, the daily dose, and the length of time the patient

has been on each medication. The patient should also be questioned about medications which have been discontinued.[8] The toxic effects of drugs may be related to the daily dosage as with certain phenothiazines,[9] or to the total dosage which the patient has received, as with chloroquine.[10] The toxic effects may be manifested at anytime after drug therapy is begun, and may continue after a drug is discontinued.[11]

The measurement of the best corrected visual acuities can be very significant in evaluating toxic reactions in certain drugs; ethambutol which is used in the treatment of tuberculosis, for example, will produce decreased visual acuities due to optic neuritis.[12] The changes must be evaluated relative to the visual acuity prior to initiating therapy since visual acuity may fluctuate in tuberculosis cases without drug therapy.[13]

Color vision testing should be performed monocularly. Drug induced optic neuritis and certain retinotoxicities will produce color vision defects particularly to red, and may occur unequally in the two eyes. Ophthalmoscopy will provide evidence of drug toxicity, which may be manifested by pigmentary deposits in the cornea, lens, and retina, (phenothiazines),[14] macular and foveal changes, vascular changes, and optic pallor (chloroquine).[15]

Visual field testing must be performed and should include testing with red as well as white targets in order to detect the earliest field changes. Baseline examinations of color vision and visual fields are often necessary in order to evaluate whether changes have occurred, and are recommended before chloroquine therapy is initiated.[17] Visual field changes can be manifested as central scotomas, peripheral contractions, or depressions.

Drug induced changes in the visual fields have commonly been referred to as toxic amblyopias and considered diseases of the optic nerve. Harrington points out that this is incorrect because the nature and site of the toxic effect is frequently not identified. He suggests that a more realistic approach to classification of drug related visual field defects would be according to the specific agents.[18]

This article will identify those drugs or classes of drugs which are most responsible for causing visual field changes. The therapeutic uses of the drugs as well as associated ocular changes will be presented. Those drugs which are now of historical interest will not be discussed.

Chloroquine

Chloroquine is a 4- aminoquinoline compound. It was originally used to treat malaria, and was later found to be useful in the treatment of rheumatoid arthritis and lupus erythematosus.[19,20] The toxic effects are related to the total dosage received.[21] Toxic effects are not generally seen until a total dose of 300 gm. has been taken.[22]

Chloroquine produces generally irreversible retinal changes. These consist of bilateral increased macular pigmentation and loss of foveal reflex, with the appearance of a dark spot in the center of the macula. This is surrounded by a depigmented ring which in turn is surrounded by a ring of increased pigmentation. The ophthalmoscopic view resembles a bull's-eye target. Vascular sheathing and arteriolar narrowing may occur as the toxicity progresses, with waxy pallor of the optic discs being observed late in the process.[23,24]

The symptoms of chloroquine retinopathy are difficulty with reading, photophobia, blurred vision, and flashing lights.[25]

Visual field changes may vary from central and ring scotomas to peripheral contractions. The characteristic field change is a large central scotoma with a small island of lesser loss centrally. An early scotoma to red and changes detected with color vision test plates are an early sign of retinal changes.[26]

It is recommended that baseline and periodic examinations be performed on patients taking chloroquine and that any unexplained changes in visual acuity, visual fields, and/or ocular pigmentation result in immediate discontinuance of the drug.[27]

Hydroxychloroquine

Hydroxychloroquine is a 4-amino quinoline which is used in the treatment of malaria, lupus erythematosus, and rheumatoid arthritis. It is pharmacologically similar to chloroquine and can produce the same clinical picture of toxicity.[28,29] The incidence of the toxic effects is reported to be less than that of chloroquine.[30]

Indomethacin

Indomethacin is a non-steroidal effective antipyretic, analgesic, anti-inflammatory agent which is used in the management of rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, and gouty arthritis.[31]

Indomethacin causes systemic complications in 35 to 50 percent of patients taking therapeutic doses and 20 percent must discontinue the drug. Patients on long term therapy report severe frontal headaches in 25 to 50 percent of the cases.[32]

Ocular side effects may include corneal opacities, visual field changes, and pallor of the optic disc.[33]

Retinal and macular disturbances may occur and may be associated with blurred vision. The changes may be asymptomatic, however, and patients on indomethacin should have periodic ocular examinations[34] including visual

acuities, ophthalmoscopy, biomicroscopy, and visual fields.

Digitalis glycosides

The digitalis glycosides are a group of drugs which are uniquely effective in the treatment of congestive heart failure, atrial fibrillation, atrial flutter, and paroxysmal tachycardia.[35] Included in this group are digoxin, digitoxin, lanatoside, and ouabain.

The incidence of ocular side effects from digitalis is as high as 25 percent.[36] Digitalis poisoning, or intoxication, is common and one of the most frequent adverse reactions seen.[37] Digitalis intoxication can occur from a single high dose or may be due to the cumulative effect of small doses.[38] Visual side effects may occur with normal doses and do not produce intoxication.[39]

The ocular symptoms of digitalis toxicity are numerous and include amblyopia, scintillating scotomas, photophobia, colored appearance to objects (red, yellow, green, blue), flashes of light, frosted appearance of objects, and colored halos around objects.[40,41]

In cases of amblyopia, bilateral central scotomas will be found on visual field testing. These scotomas may be due to either retinal effects or retrobulbar optic neuritis.[42] Research has indicated that the visual effects of digitalis may be related to inhibition of enzyme mechanisms responsible for repolarization of cone receptors.[43,44]

The visual toxic effects of digitalis usually disappear within two weeks after drug discontinuance.[45]

Quinidine

Quinidine is an isomer of quinine which is useful in the treatment of premature atrial ventricular contraction, paroxysmal atrial and ventricular contraction, paroxysmal atrial tachycardia, and atrial flutter.

The ocular side effects are infrequent and may include blurred vision, color vision defects, night blindness, diplopia, photophobia and neuritis.[46]

Visual field defects may be scotomas or constrictions of the field.[47]

Ethambutol

Ethambutol is a drug which is used in the treatment of active pulmonary tuberculosis.[48] Ethambutol produces symptoms of blurred vision and color vision defects which appear to be due to drug induced optic neuritis.[49] The changes in visual acuity may be unilateral or bilateral.

Baseline visual acuities and periodic examination is mandatory in order to evaluate the toxic effects of ethambutol. Changes in visual acuity must be evaluated with regard to the initial best corrected acuity as determined during baseline studies (see table, page 972, *Physicians' Desk Reference,* 1979).

Visual fields should also be evaluated during baseline and follow-up visits. Defects of visual fields due to ethambutol may include central or annular scotomas, constrictions, and hemianopsias.[50]

Any changes of visual acuity or visual fields not attributable to other causes would be indications for discontinuing ethambutol therapy. The toxic effects are related to daily dose and duration of treatment, and are generally reversible if therapy is promptly discontinued.

Isoniazid

Isoniazid is the most useful drug available in the treatment of actively growing tuberculosis bacilli.[51]

The significant ocular side effects of isoniazid are those which are neurophthalmic. Decreased vision, optic neuritis, optic atrophy and papilledema have been observed. Visual field defects caused by isoniazid include scotomas, constrictions, and hemianopsias.[52] Discontinuing the drug results in reversal of the side effects.[53]

Chloramphenicol

Chloramphenicol is a broad spectrum antiobiotic which is used to treat serious infections which do not respond to less hazardous therapeutic agents, and is used in the treatment of cystic fibrosis.[54]

The ocular side effects of chloramphenicol are decreased visual acuity,[55] optic neuritis, and edema of the optic discs,[56] retrobulbar neuritis, and optic atrophy.[57] Bilateral central scotomas and constrictions have been observed. The ocular side effects are common in children, but not in adults treated with systemic chloramphenicol.[58]

Streptomycin

Streptomycin is an antibiotic which is useful for treatment of Mycobacterium tuberculosis and serious non-tuberculosis organisms.

Streptomycin is a neurotoxic drug which can affect the optic nerve, auditory nerve, and cause peripheral neuritis, arachnoiditis, and encephalopathy.[59] The ocular side effects include decreased vision, nystagmus, and retrobular or optic neuritis. Visual field defects reported with streptomycin include central scotomas and enlarged blindspots.[60] The toxic effects are rare and reversible in most instances.

Thioridazine

Thioridazine is one of the many phenothiazine derivatives, which include chlorpromazine, promethazine, and trifluoperazine. They are among the most widely used drugs and are useful in the management of psychotic disor-

ders, depression, and anxiety neuroses, and symptoms associated with organic mental syndrome in the geriatric patient.[61]

The side effects of phenothiazines occur in approximately 3 percent of patients, but can cause ocular side effects in up to 100 percent of patients if therapy continues more than ten years. The side effects are dependent on daily dosage and the specific phenothiazine derivative.[62]

Thioridazine can cause decreased visual acuity and pigmentary degeneration of the retina.[63] The visual field changes associated with thioridazine are central and ring scotomas, and peripheral contractions. These visual field defects may be transient or permanent.[64]

Conclusion

This paper has reviewed the role of the optometrist in evaluating drug toxicities which may affect the visual fields. Specific drugs have been cited which are most significant in inducing visual field defects. As ever increasing numbers of therapeutic agents are introduced, the practitioner must maintain an awareness of their potential for ocular side effects and utilize all clinical procedures necessary to evaluate these. **AOA**

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REFERENCES

1. Fingl E, Woodbury DM: General principles, in Goodman LS, Gilman A (eds): *The Pharmacological Basis of Therapeutics,* ed 4. New York, Macmillan, 1970.
2. *Ibid,* pp 25-26.
3. Walsh FB, Hoyt WF: *Clinical Neuro-Ophthalmology,* ed 3. Baltimore, Williams & Wilkins, 1969, p 2538.
4. *Ibid,* p 2564.
5. Fraunfelder FT: *Drug-Induced Ocular Side Effects and Drug Interactions.* Philadelphia, Lea & Febiger, 1976, p ix.
6. Walsh FB, Hoyt WF, p 2538.
7. Greenseid DZ, Leopold IH: Toxic retinopathies, (chapter 33) in Duane TD (ed): *Clinical Ophthalmology,* vol 3. Hagerstown, Md., Harper & Row, 1976.
8. *Ibid,* p 2.
9. *Ibid,* p 6.
10. *Ibid,* p 2.
11. Walsh FB, Hoyt WF, p 2538.
12. *Physicians' Desk Reference,* ed 33. Oradell, NJ, Medical Economics Co., 1979, p 972.
13. *Ibid.*
14. Fraunfelder FT, p 67.
15. Walsh FB, Hoyt WF, pp 2546-2548.
16. Greenseid DZ, pp 1-2.
17. *Physicians' Desk Reference,* pp 1842-1843.
18. Harrington DO: *The Visual Fields,* ed 4. St. Louis, CV Mosby, 1976, p 215.
19. Walsh FB, Hoyt WF, pp 224-225.
20. Greenseid DZ, p 2.
21. Walsh FB, Hoyt WF, p 2546.
22. Greenseid DZ, p 2.
23. Walsh FB, Hoyt WF, p 2546.
24. Greenseid DZ, pp 2-3.
25. Harrington DO, p 227.
26. *Ibid.*
27. *Physicians' Desk Reference,* p 1842.
28. Walsh FB, Hoyt WF, p 2548.
29. Fraunfelder FT, pp 31-32.
30. Walsh FB, Hoyt WF, p 2548.
31. *Physicians' Desk Reference,* p 1173.
32. Woodbury DM: Analgesic-antipyretics, anti-inflammatory agents, and inhibitors of uric acid synthesis, in Goodman LS, Gilman A (eds): *The Pharmacological Basis of Therapeutics,* ed 4. New York, Macmillan, 1970.
33. *Ibid,* p 338.
34. *Physicians' Desk Reference,* p 1173.
35. Goth A: *Medical Pharmacology,* ed 9. St. Louis, CV Mosby, 1978, p 390.
36. Harrington DO, pp 224-225.
37. Goth A, p 390.
38. Walsh FB, Hoyt WF, p 2543.
39. Harrington, DO, pp 224-225.
40. Fraunfelder FT, pp 161-162.
41. Greenseid DZ, p 8.
42. Harrington DO, p 225.
43. Walsh FB, Hoyt WF, p 2544.
44. Greenseid DZ, p 8.
45. Harrington DO, p 224.
46. *Physicians' Desk Reference,* p 1052.
47. Fraunfelder FT, p 148.
48. *Physicians' Desk Reference,* pp 971-972.
49. Fraunfelder FT, p 43.
50. *Ibid.*
51. Weinstein L: Drugs used in the chemotherapy of leprosy and tuberculosis, in Goodman LS, Gilman A (eds): *The Pharmacological Basis of Therapeutics,* ed 4. New York, Macmillan, 1970.
52. Fraunfelder FT, p 45.
53. Weinstein L, p 1327.
54. *Physicians' Desk Reference,* p 1277.
55. Fraunfelder FT, p 10.
56. *Physicians' Desk Reference,* p 1278.
57. Harrington DO, p 225.
58. Fraunfelder FT, p 10.
59. *Physicians' Desk Reference,* p 1057.
60. Fraunfelder FT, p 23.
61. *Physicians' Desk Reference,* p 1505.
62. Fraunfelder FT, p 68.
63. Walsh FB, Hoyt WF, p 2636.
64. Harrington DO, pp 229-230.

1980 Editors Contest Award Winners

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Best National Magazine — *Journal of Optometric Education,* Harriet E. Long, editor.

Best Newsletter — *Optometry Forum,* University of California Optometry Alumni Association; second place, *OEP News,* Mary Kay Aufrance, editor.

Best Editorial — "Why Are We Afraid to Change?" by D. Burkett Nelson, O.D., *Tennessee Optometrist,* September, 1979; second place, "Ophthalmic Placement Test" by Bob Day, Jr., O.D., *Texas Optometry.*

Best Original Article — "Evaluation of Neurological Dysfunction as Related to the Visual System," by Beckwith Steiner, O.D., *Texas Optometry,* October and November, 1979; second place, "Helping Children Learn — AB 1250 Lets O.D.s Help," *California Optometry,* August 1979.