VISUAL EVOKED RESPONSES IN TUBERCULOUS CHILDREN ON ETHAMBUTOL THERAPY

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ABSTRACT

Visual evoked responses (VERs) were recorded in 47 children, aged 3-13 years with tuberculosis, treated with ethambutol (20 mg/kg/day) as a part of the antitubercular regimen. VERs were evoked by monocular whole field stimulation, the stimulus being provided by a black and white checker-board pattern reversed every 560 msec and recorded before the commencement, 2, 4, 6, 9 and 12 months of therapy and between 3 to 6 months after stopping the drug. In the first 6 months of therapy the mean values of latency ranged from 92.8 to 101.3 msec in the 3 to <6 years age group and 88.5 to 100.3 msec in children 6-13 years of age. Between 6-12 months of therapy the mean values of latency were between 93.3 to 101.0 msec in the 3 to <6 years age group and 96.0 to 101.5 msec in the older group. Between 3-6 months after stopping therapy the means of latency ranged from 92 to 96 msec. The differences were not statistically significant at any point of time.

Thus, children do not seem to be at greater risk for developing ethambutol inducted optic damage as compared to adults. Ethambutol in the above stated dose may, therefore, be recommended for inclusion in antitubercular chemotherapy in pediatrics without undue fear of subclinical toxicity.

Key words: *Ethambutol, Visual evoked responses, Subclinical toxicity.*

Ethambutol, a dextrorotatory isomer of 2-2'-(ethylene di-imino)-di-1-butol, an orally administered anti-tubercular agent has largely replaced paraminosalicylic acid in the chemotherapy of tuberculosis. Carr and Henkind were the first to report reversible toxic amblyopia by this drug(1). The adverse effects included loss of central vision associated with central scotoma, marked decrease in color discrimination and defect in the peripheral visual field isotopers. In view of the practical difficulties associated with assessment of these parameters in children, the use of ethambutol has been very restricted in pediatric antitubercular chemotherapy. Visual evoked response (VER) is an electrical activity appearing in the EEG with the appearance, disappearance or change of a visual stimulus(2).

In patients with optic neuritis, the VER of the involved eye has an increased latency period and a decreased amplitude compared to normals. This occurs even when no decrease in visual acuity, color perception, or visual field defect can be detected(2). Yiannikas has recommended the use of VER for routine monitoring of ocular function in patients on ethambutol as a measure of early detection of subclinical toxic optic effects(3).

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Received for publication April 23, 1990; Accepted August 20, 1990

The objective of the present investigation was to study the VER in children who were given ethambutol as part of their antitubercular regimens.

Material and Methods

VER is an electrical activity appearing in the EEG with the appearance, disappearance or change of a visual stimulus. The subject is visually stimulated repeatedly and the computer averages the electrical activity generated at specific sites over the scalp for a specific period following each stimulation. Activity which is a direct result of stimulation will accumulate to produce the evoked response(4). VERs are recorded from scalp electrodes which may be placed anywhere but always include the posterior occipital area. Stimulation may be a flash of diffuse light discrete light or a patterned stimulus, *e.g.,* an illuminated checkerboard. The stimuli are repetitively presented randomly or regularly within a short period of time, *e.g.,* 1 cps for 100 sec. The computer averages the subsequent electrical activity and the evoked response is recorded graphically by an X-Y plotter or photographically from an oscilloscope.

The latency and amplitude of the various components of the resulting evoked response recorded at the occiput reflect the conduction time and the mass conduction along the visual pathways to the occipital cortex as well as the activity from the extrastriate cortex that possibly correlates with the processing of visual informations(4). The pattern of the normal VER is constant (*Fig. 1*).

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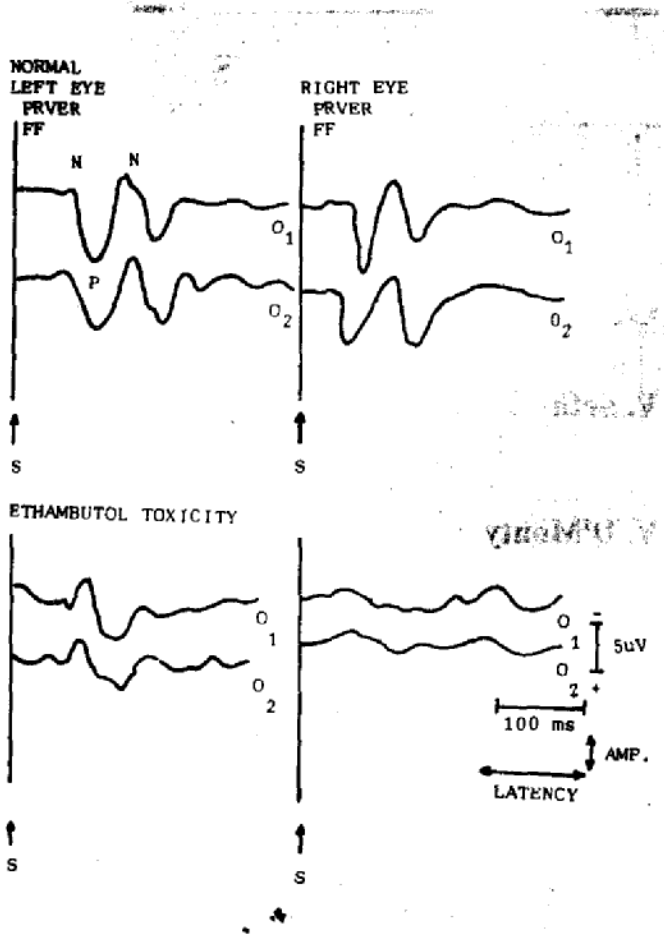

Fig. 1. Schematic VER record after full field pattern reversal stimulation (FF, PRVER) in normal eyes and those affected by Ethambutol toxicity. S=Stimulus; P=Postitivity; N=Negativity; AMP=Amplitude.

acuity, color perception, or visual field defect. As the optic nerve recovers, amplitude may return to normal, but the latency period continues to be prolonged(4).

VER was studied in 47 children, suffering from pulmonary tuberculosis. These children were divided into Group I between 3-6 years of age (27 children) and Group II between 6-13 years of age (20 children). Their optic fundi showed no tubercular involvement on ophthalmic examination. They were administered ethambutol in a dose of 20 mg/kg/day as a part of their antitubercular regimen. VER was evoked by monocular whole field stimulation, the stimulus being provided by

a black and white checkerboard pattern reversed every 560 msec and recorded before the commencement, and at 2, 4, 6, 9 and 12 months of therapy and between 3-6 months after stopping the drug. Due to the practical difficulties involved in the ideal case of repeatedly testing the same patient 6 times during the 1½ years follow-up period, all patients in each group were not followed up for the full period. Also, the patients on whom VER was done were not necessarily the same at different time intervals. Ten children who were not on ethambutol therapy served as controls. The difference in latency and amplitude were statistically analyzed by Students 't' test using $p<0.05$ as the cut-off value.

Results

In the first 6 months of therapy the lowest reading for mean value of latency was 92.8 msec in the 3 to <6 years age group (Group I, *Table I*) and 88.5 msec in children 6-13 years of age (Group II, *Table II*). In the same period the highest reading for mean value of latency was 101.3 msec in Group I and 100.3 msec in Group II. At 6 months to 1 year of therapy the lowest reading for the same was 93.3 msec in Group I and 96.0 msec in Group II, while the highest reading was 101.0 msec in Group I and 101.5 msec in Group II. Between 3 to 6 months after cessation of therapy the minimum and maximum values for the mean of latency was 94 and 96 msec (Group I) and 92 to 94 msec (Group II), respectively. The difference in latencies was not statistically significant at any point of time both during and after therapy.

Discussion

Ethambutol is known to cause visual impairment due to optic neuritis which is dose related and usually reversible(3). Liebold(5) described two types of retrobulbar neuritis which usually affected both eyes. Patients with central or axial toxic effects had reduced visual acuity, impaired color vision and a central scotoma. Those with periaxial toxic effects had a defect in peripheral isotopers of their field, with little or no decrease in visual acuity and

TABLE I—*Mean VER at Difference Intervals of Therapy at 3 to <6 years of Age (Group I)*

Duration of therapy in months (±1 wk)	No. of patients	Mean VER ± SD			
		Right eye		Left eye	
		Amp	Latency msec	Amp mv	Latency msec
2	5	12.57 ± 5.56	99.67 ± 6.36	11.83 ± 4.52	101.33 ± 2.21
4	5	10.44 ± 5.46	97.20 ± 2.77	8.86 ± 3.52	97.40 ± 2.68
6	5	10.84 ± 5.02	92.80 ± 4.09	11.80 ± 4.77	97.86 ± 4.21
9	4	9.87 ± 4.14	101.00 ± 8.70	11.20 ± 6.06	93.70 ± 15.22
12	4	8.50 ± 1.76	93.30 ± 1.41	9.66 ± 4.31	97.50 ± 11.31
15-18	3	12.20 ± 4.58	94.00 ± 4.24	10.00 ± 3.82	96.00 ± 6.82
Normal controls	5	8.00 ± 1.20	92.80 ± 5.65	7.30 ± 3.18	92.00 ± 11.30

$P>0.05$ in all cases.

TABLE II—*Mean VER at Difference Intervals of Therapy at 6-13 years of Age (Group II)*

Duration of therapy in months (±1 wk)	No. of patients	Mean VER ± SD			
		Right eye		Left eye	
		Amp mv	Latency msec	Amp mv	Latency msec
2	5	12.65 ± 2.26	97.50 ± 7.24	11.55 ± 1.72	95.50 ± 4.28
4	3	13.80 ± 4.14	100.30 ± 11.60	13.40 ± 4.52	97.30 ± 2.83
6	4	4.65 ± 2.79	88.50 ± 6.12	5.00 ± 2.03	92.00 ± 0.00
9	3	5.60 ± 0.76	101.50 ± 13.40	6.40 ± 1.78	01.00 ± 26.82
12	3	6.30 ± 0.98	96.00 ± 18.38	5.60 ± 0.70	87.00 ± 24.04
15-18	3	12.30 ± 0.96	92.00 ± 1.00	12.70 ± 2.62	94.00 ± 4.35
Normal controls	5	9.00 ± 4.20	91.60 ± 1.20	8.10 ± 3.72	95.00 ± 7.78

$p > 0.05$ in all cases

normal color vision. However, the exact mechanism by which ethambutol produces retrobulbar neuritis is unknown(3). Animal studies have shown that the drug can cause depletion of copper and zinc, with concomitant decrease in cytochrome C oxidase activity(5). The optic neuritis may be a direct toxic effect on the retina due to an abnormality in zinc metabolism possibly brought about by chelation of zinc by ethambutol(7). It has also been postulated that ethambutol being a butanol derivative, may cause toxic amblyopia by a mechanism similar to that of alcohol(8). The visual side effects usually occur weeks or months after starting treatment(9,10).

Factors which are known to predispose to ethambutol toxicity include impaired renal function, diabetes and optic neuritis related to tobacco and alcohol(11). These rarely operate in children. Animal studies have shown that the areas most vulnerable to the toxic effects of the drug were the optic nerves, chiasma and tracts. Demyelination of the optic nerve fibers was prevalent but axis cylinders and fiber boundaries were generally intact(12).

The incidence of optic neuritis is dose related(9) and is negligible at a dose of 15 mg/kg(13,14). However, studies in patients using doses ranging from 15-25 mg/kg have reported complications in 1.6-2.84% of the cases in adults(8,9,15). Despite intensive literature survey by the authors, no studies on VER in children on antitubercular regimens containing ethambutol are available for comparison.

There was no statistically significant change in either amplitude or latency of the VER at any point of time in both age groups in our study where ethambutol was administered in a dose of 20 mg/kg.

The VER is useful in children as it detects minimal/subclinical disturbances in optic nerve conduction with commendable accuracy. Furthermore, it is useful in monitoring cases of ocular toxicity as it documents the reversibility of these disturbances with cessation of ethambutol therapy(16). Ethambutol now has a place as a good antitubercular drug. It is bactericidal in the first few days of treatment(17) and is also useful in cases of drug resistant tuberculosis and opportunistic mycobacterial in-

fections with or without HIV positivity as a companion to isoniazid and rifampicin(18). In the years 1963-1987 one death was reported to the Committee on Safety of Medicines in UK in relation to ethambutol as compared to 26 each attributed to rifampicin and isoniazid and 7 to pyrazinamide. In the same period, ethambutol was linked to 4 cases of blindness(18). In our study, ethambutol administration in a dose of 20 mg/kg produced no significant change in any modality of VER. Hence, we recommend its usage as a routine antitubercular drug in pediatric practice with less fear of toxic reactions, provided appropriate dosage schedules are strictly adhered to.

REFERENCES

1. Carr RE, Henkind P. Ocular manifestations of ethambutol. Arch Ophthalmol 1962, 67: 566-571.
2. Rosenberg MA. Visual evoked response *In:* Principles and Practices of Ophthalmology, Vol III. Eds. Peyman GA, Saunders DR, Goldberg MF. Tokyo, WB Saunders Company. 1980, pp 1928-1930.
3. Yiannikas C, Walsh JC, McLeod JG. Visual evoked potentials in the detection of subclinical optic toxic effects secondary to ethambutol. Arch Neurol 1983, 40: 645-648.
4. Galloway NR. Opthalmic electrodiagnosis. *In:* Major Problems in Opthalmology, Vol. I, 2nd edn. Ed Patrick DTR. London, Lloyd Luke Ltd. 1981, pp 29-40.
5. Liebold JE. The ocular toxicity of ethambutol and its relation to dose. Ann NY Acad Sci 1966, 135: 904-909.
6. Campbell JA, Elmes PC. Ethambutol and the eye: Zinc and Copper. Lancet 1975, 2: 711.
7. Lesell S. Histopathology of experimental intoxication. Invest Opthalmol 1976, 15(a): 765-768.
8. Roberts SM. A review of the papers on the ocular toxicity of ethambutol hydrochloride (Myambutol) an antituberculosis drug. Am J Optom Physiol Opt 1974, 51: 982-987.
9. Citron KM. Ethambutol–A review with special reference to ocular toxicity. Tubercle 1969, 5 (Supple):32-36.
10. Barron GJ, Tepper L, Lovine G. Ocular toxicity from ethambutol. Ann J Opthalmol 1974, 77: 256-266.
11. Murray FJ. US Public Health Service experience with ethambutol. Vienna, International Congress of Chemotherapy. 1967, 6: 339.
12. Schmidt IG. Central nervous system: effects of ethambutol on monkeys. Ann NY Acad Sci 1966, 135: 759-774.
13. British Thoracic and Tuberculosis Association. Short course chemotherapy in pulmonary tuberculosis. Third Report. Lancet 1980, 1, 1182-1183.
14. Fox W. Short course chemotherapy for tuberculosis. *In:* Recent Advances in Medicine, Vol 19. Ed Saunders KB. London, Pitman. 1983, pp 307-326.
15. Roussos T, Tsolkas A. Toxicity of myambutol on human eye. Ann Ophthalmol 1970, 2: 577-580.
16. Petrera JE, Fledelius HC, Trojaborg W. Serial pattern evoked potential recording in a case of toxic optic neuropathy due to ethambutol. Electroencephalograph. Clin Neurophysiol 1988, 71: 146-149.
17. Chaulet P. Treatment of Tuberculosis: Case Holding Until Cure. Geneva, World Health Organization, WHO/TB/83. 141, Rev. 2, p 9.
18. Campbell IA, Ormerod LP. Ethambutol and the eye. Lancet 1988, 2: 113-114.