OCULAR TOXICITY FROM ETHAMBUTOL

Y C Chee

Department of Medicine III
Tan Tock Seng Hospital
Moulmein Road
Singapore 1130

Y C Chee, MBBS, M.Med, MRCP (UK)
Registrar

SYNOPSIS

Seven patients on treatment for tuberculosis with Streptomycin, Ethambutol and Isoniazid developed retrobulbar neuritis with blindness out of approximately 1382 cases followed up between June 1977 and December 1979. Although there is no way to prove conclusively that Ethambutol is responsible, it is the most likely cause. Clinical features of these patients, their treatment and prognosis are presented and discussed. Reversibility of blindness occurred in only three of these seven patients.

INTRODUCTION

Ethambutol (EMB) is a synthetic compound with mainly bacterostatic anti-tuberculous activity. It is remarkably well tolerated by patients of all ages including pregnant patients, and alcoholics, even those with cirrhosis or alcoholic neuropathy. It is not contraindicated in diabetes. With the exception of ocular complications, no toxicity has been convincingly attributed to EMB in man.

MATERIAL AND METHOD

From departmental statistics, 1382 new cases of tuberculosis (mainly pulmonary) were seen and treated at the outpatient chest clinic between June 1977 and December 1979. Patients developing visual problems while on EMB were referred to The Eye Clinic for further investigations. Seven patients developed ocular complications attributable to EMB. Salient clinical features of these patients are presented in the following table.

Table: Clinical Summary of Seven Patients

Patient	Sex/Age(Yr)/Race	Blood Urea (Normal 20 to 40mg%)	Duration on EMB before symptoms occurred	Follow-up (months)	Outcome
1	M/20/Chinese	normal	46 days	30	Poor
2	M/69/Chinese	95; 50mg%	72 days	6	Poor
3	M/58/Chinese	normal	72 days	18	Poor
4	F/54/Malay	78mg%	259 days	14	Poor
5	M/59/Chinese	normal	140 days	18	Good
6	F/65/Chinese	60mg%	11 months	4	Good
7	M/22/Chinese	normal	15 months	25	Good

All these patients had the standard chemotherapy regime consisting of Streptomycin injections ½ - 1 gram daily, oral Isoniazid 300 mg. daily and oral EMB at a dose of 25mg/kg/day for the initial eight weeks then at 15mg/kg/day till the end of treatment. The moment visual symptoms thought related to EMB were noted, the drug was stopped; the patients' visual acuity tested and if impaired, the ophthalmologist took over for further assessment and management. The drug regimen for tuberculosis was then modified with EMB omitted. These seven patients were all diagnosed as EMB induced optic neuritis.

Two female and five male patients with ages ranging from 20 to 69 years developed EMB induced optic neuritis. All were Chinese except for one Malay lady. Three had raised blood urea levels. They were elderly and both the females were in this group. Four patients, despite normal renal function had visual impairment and of the two young males in their twenties, only one recovered. Duration while on chemotherapy before the onset of visual symptoms ranged from 46 days to 15 months. Those with raised blood urea did not appear more prone to develop this complication after a shorter duration on EMB. Also young age and normal renal function did not preclude this complication occurring. For recovery, follow-up ranged from 4 to 30 months. The four patients with poor outcome remained so even though the longest duration after ceasing EMB was 30 months. Comparing these with the other three, it appears that those who develop symptoms of toxicity after being on EMB for a shorter duration tend to have a poorer prognosis.

Therefore no age or sex is exempted from EMB optic neuritis. Renal dysfunction although a predisposition, need not be present. It is not possible to predict who will develop this complication but it is prudent to decrease the dose of EMB if renal impairment exists. Prognostically, contrary to what is hoped for and expected, the optic neuritis is not always reversible.

DISCUSSION

The anti-tuberculous activity of EMB was first reported in 1961 by Thomas et al who also established that the biological activity of the racemic mixture was totally accounted for on the basis of the dextro isomer. The first clinical studies were conducted with the racemic mixture, and severe toxic ocular symptoms were reported by Carr and Henkind (5) and by Carr (4) when this dextro isomer was used. Subsequent investigations with the dextro isomer by Bobrowitz and Gokulanathan (2), Bobrowitz et al (3), Corpe et al (7), Place and Thomas (13) and Pyle et al (14) indicate a lower incidence of eye toxicity than that reported for the racemate. These investigations found a reversible, reduced visual acuity in a limited number of patients.

Retrobulbar optic neuritis is a well established hazard of EMB therapy in man. Liebold (9) reviewed this subject and distinguished two types of neuritis. The most frequent is that in which central fibres of the optic nerve are involved. Vision becomes blurred and examination reveals diminished visual acuity, a central scotoma and usually loss of ability to see green and sometimes red also. In the second less common type, the peripheral fibres of the optic nerve are involved. There may be no visual disturbance or fall in visual acuity. However, examination reveals constriction of peripheral fields of vision. In both types, the fundi and discs appear normal. The latter type more usually results from EMB dosage above 30mg/kg. Optic toxicity normally occurs after the first two months of therapy. Citron (6) quoted the makers of EMB reporting 31 patients who had subjective visual disturbance of whom 23 recovered, three (10%) partially recovered and five (16%) had not improved at the last time of follow-up (length of follow-up not given). Of 44 patients with objective ocular signs, 24 recovered, 8 (18.2%) partially recovered and 12 (27.3%) had not recovered at the time of follow-up. Further one patient who continued the drug for one month after the onset of subjective ocular symptoms became completely blind. Thus in these two sets of patients, 26% and 45.5% did not recover completely but the dosage of EMB in these patients was not reported.

There is clear cut evidence that the incidence of retrobulbar neuritis is dose-related. The incidence was 15% among 60 patients given 50mg/kg (8) and 18% among 59 patients given doses greater than 35mg/kg (9). It was 5% among 59 patients given doses less than 30mg/kg (9) and 3% among 130 patients given 25mg/kg (15). Citron (6) observed 34 patients receiving 25mg/kg daily for up to 2 years with repeated eye studies throughout and found two patients with confirmed retrobulbar neuritis (6%). The present series gives a very low incidence of 0.5% (7 out of 1382 cases). Murray (10) reported the U.S. Public Health Service Study as suggesting that the incidence of optic toxicity attributed to EMB is negligible when using 15mg/kg dose.

EMB orally is rapidly absorbed and the rate of absorption is not altered when given with meals. About 10% is metabolished and most of the rest excreted unchanged in the urine (11). No drug accumulation occurs with consecutive single doses of 25mg/kg in patients with normal kidney function but renal insufficiency may lead to accumulation. Three of the seven cases reported here had raised blood urea and this, only slightly so. All these three are past 50 years old. The other four are all males with normal renal function, two of whom are young yet they had visual disturbance - one probably with permanent blindness. Normal renal function does not therefore prevent this complication. It may be of interest to note that Liebold (9) could find no common factors among his cases of EMB toxicity except that all of them were males. Thus despite low dosage and normal renal function, EMB toxicity still occurs.

To reduce the dose of EMB below 15mg/kg would sacrifice therapeutic efficacy. Routine visual acuity tests or other eye examination during treatment would be of value if they could reveal abnormality before visual disturbance is evident to the patient. Liebold (9) mentioned that it is unnecessary to have periodic visual field studies on those taking less than 30mg/kg/day as the blurred vision and loss of ability to see green colours have always been present together and have appeared concurrently. Citron (6) expressed

similar views so that in practice, routine visual acuity testing during EMB therapy serves no useful purpose since they fail to detect ocular toxicity before symptoms occur and may not be abnormal even when symptoms are present. Further a small change in visual acuity may not be the result of EMB ocular toxicity.

Place et al (12) analysed five patients with EMB toxicity from a series of 23 patients. They concluded that the recovery time was related to the severity of the defect and that recovery could be completed even after repeated episodes of impaired vision. The present series is at variance with the latter in that four patients have not improved after long follow-up.

Once EMB optic neuritis is suspected the drug is discontinued immediately. Treatment by the ophthalmologist consisted of steroids and vitamins A and B. Steroids were given as retrobulbar injections of dexamethasone or methyl prednisolone, as oral prednisolone or intramuscular A.C.T.H. in various regimes. All the seven did not have exactly the same treatment; neither was steroids used in all. The three that improved received retrobulbar steroids but two of the four that did not improve also received these injections. It is difficult to evaluate the efficacy of these injections as EMB optic neuritis is known to spontaneously recover.

The exact mechanism by which EMB produces retrobulbar neuritis is unknown. Repeated attacks of this condition are more likely to produce permanent changes in the optic nerves than the initial attack (9). This contrasts with the conclusion of Place et al (12). However with the many drugs available today for treating tuberculosis, there is no indication to exhibit EMB on the same patient again once visual abnormalities develop. Experiments on monkeys done by Schimdt (16) showed that areas of the central nervous system most vulnerable to the toxic effects of EMB were the optic chiasma, optic tracts and optic nerves. Doses of the drug at 800 mg/kg/day caused lesions in the centre of the optic chiasm either in an early or moderately advance state of degeneration consisting of early or more pronounced demyelination of optic fibres with proliferating microglia. As this dose is never used in man, and EMB optic neuritis is reversible in some cases, it is likely that those affected are inherently susceptible to demyelination and in those that do not recover, the demyelination has progressed too far and glial proliferation has occurred. The use of steroids in treating demyelinating diseases of the central nervous system is unresolved at present, but in desperate situations and with no contraindications, a trial of steroid therapy could be given.

CONCLUSION

EMB optic neuritis is rare in Singapore at the doses prescribed. Periodic visual testing is unnecessary. Unless renal impairment is severe, 15-25mg/kg/day of EMB would not be harmful in the majority of patients. However, every patient receiving EMB should be warned that if visual symptoms become manifest, the drug should be stopped and an ocular examination undertaken. Impaired vision may returned to normal but not necessarily so. With modern trends in tuberculous chemotherapy toward short course regimens where EMB is not one of the drugs used, optic neuritis would not occur.

REFERENCES

1. Annual Report for 1979, Department of Medicine III, Tan Tock Seng Hospital, Singapore.
2. Bobrowitz I D & Gokulanathan S: Ethambutol in the treatment of pulmonary tuberculosis. Abstr 8th Int Congr Dis Chest Oct. 11-15, Mexico City, 1964.
3. Bobrowitz I D, Garber M & Sukumalchentra Y: The use of Ethambutol in pulmonary tuberculosis. Trans. 22nd Res. Conf. Pul. Dis. U.S. Veterans Admin., Dept. Med. Surg., Washington D. C. 1963; 254-261.
4. Carr R E: Racemic isomer of ethambutol. Arch ophth 1962; 68: 718.
5. Carr R E, Henkind P: Ocular manifestations of ethambutol: Toxic amblyopia after administration of an experimental anti-tuberculous drug. Arch ophth 1962; 67: 566-571.
6. Citron K M: Ethambutol: A review with special reference to ocular toxicity. Tubercle 1969; 50: Supp. 32-36.
7. Corpe R F, Blalock F A, Gross J A, Goldhammer E J: Retreatment of drug.resistant cases of pulmonary tuberculosis at Battey State Hospital. Amer Rev Resp Dis 1964; 90: 957-962.
8. Kass I: Chemotherapy regimens used in retreatment of pulmonary tuberculosis. Part II. Observations on the efficacy of combination of ethambutol, capreomycin and companion drugs. Tubercle 1965; 46: 166-177.
9. Liebold J E: The ocular toxicity of ethambutol & its relation to dose. Ann N Y Acad Sci 1966; 135: 904-909.
10. Murray F J: U.S. Public Health Service experience with ethambutol. International Congress of Chemotherapy, Vienna 1967; 6: 339.
11. Peets E A, Sweeney W M, Place V A, Buyske D A: The absorption, excretion and metabolic fate of ethambutol in man. Am Rev Resp Dis 1965; 91: 51-58.
12. Place V A, Peets E A, Buyske D A, Little R R: Metabolic and special studies of ethambutol in normal volunteers and tuberculous patients. Ann N Y Acad Sci 1966; 135: 775-795.
13. Place V A, Thomas J P: Clinical pharmacology of ethambutol. Am Rev Resp Dis 1963; 87: 901-904.
14. Pyle M M, Pfuetze H K, Pearlman M D, De La Heurga J, Hubble R H: A 3 year clinical investigation of ethambutol, a new anti-mycobacterial drug: Efficacy, toxicity and bacterial resistance. Abstr 8th Int Congress Dis Chest Oct. 11-15, Mexico City, 1964.
15. Pyle M M, Pfuetze H K, Pearlman M D, De La Heurga J, Hubble R H: A 4 year clinical investigation of ethambutol in initial and re-treatment cases of tuberculosis: Efficacy, toxicity and bacterial resistance. Am Rev Resp Dis 1966; 93: 428-441.
16. Schimdt L H: Studies on the anti-tuberculous activity of ethambutol in monkeys. Ann N Y Acad Sci 1966; 135: 747-774.