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ETHAMBUTOL INDUCED OCULAR TOXICITY IN PAEDIATRICS: A REVIEW OF LITERATURE

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Abstract:

SETTINGS: Review of the literature on the use of ethambutol in children based on Med- line and other sources.
OBJECTIVES: Ethambutol's most well-known side effect is ocular toxicity. As a result, its use among children is generally discouraged. The current article summarises the research on this topic.
RESULTS : There have been no reports of serious ocular side effects in children treated with ethambutol.
CONCLUSION: For children aged 5 years or older, ethambutol at a dose of 15 mg/kg/day can be recommended for routine treatment with no additional precautions than for adults; this should be included in official recommendations. Ethambutol can also be used without concern for side effects in younger children.

KEYWORDS : ethambutol, toxicity, ocular, children

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INTRODUCTION:

The synthetic substance 2,2'-ethy1enediimino-di-1-butanol dihydrochloride isomer is called ETHAMBUTOL. In 1961, it was found to have action against Mycobacterium tuberculosis. Although they needed greater dosages and were more toxic than dextro, other isomers were first used as well; ocular adverse complications were relatively regularly observed. [1, 2]

Ethambutol has always been thought of as a bacteriostatic drug, although some research suggest that at dosages of 25 mg/kg or greater, it exhibits bactericidal activity[3]. 20% of an oral dose is excreted in the faeces, 10% is converted to an inactive form by metabolism, and the remaining 60% to 70% is eliminated unchanged in the urine. The dose must be decreased in cases where the kidneys are not functioning properly[4].

Retro-bulbar optic neuritis, which can take one of two different forms, is the most harmful toxic side effect of ethambutol. [5-7] The more prevalent variety is connected to dosage and course of therapy, and is typically reversible: [8,9] the optic nerve's core fibres are most frequently damaged, which results in impaired vision, decreased visual acuity, central scotomas, and frequently a loss of the capacity to perceive green and occasionally red. The peripheral fibres of the optic nerve are involved in the more rare type of ocular poisoning. Although evaluation reveals peripheral constriction of the visual fields, visual acuity and colour vision may not be impacted. On ophthalmoscopic examination, the fundus seems normal because the neuritis is retrobulbar in both forms. [8]

Ethambutol dosage for adults has been changed[10] and is now 15 mg/kg/day, regardless of the stage of treatment (or 30 mg/kg three times per week or 45 mg/kg twice per week). Up until recently, the majority of doctors prescribed it at a dose of 25 mg/kg/day for the first two months, followed by 6 to 10 months at 15 mg/kg/day. It has been frequently utilised in clinical trials, especially those run by the British Medical Research Council, in both industrialised and developing nations (MRC). A review of these trials[11], in which ethambutol was administered for 2 to 12 months, reveals 10 instances of ocular toxicity in 2184 individuals without any lasting effects. In trials conducted in the USA (304 patients)[12] and Canada (421 patients),[7] ocular complications occurred in 1% of cases (respectively 3 and 4 cases), and in 2 of those cases, the changes were irreversible: one case experienced a minor alteration of ocular functions, and the other received the product at a higher dosage than advised (35 mg/kg daily for 4 months). One case with severe visual sequelae after only 6 days of ethambutol at 1J mg/kg[14] has been reported. Isolated cases of retrobulbar neuritis described in the literature[13] typically involve long-term usage and often higher dosage than recommended.

Children are less likely to self-report symptoms of ocular toxicity after using ethambutol, which makes it more difficult to diagnose ocular toxicity (visual acuity tests, colour discrimination and visual fields).

Research involving ophthalmological follow-up

In India, 47 children[15] with tuberculosis (27 aged 3–5 years and 20 aged 6–13 years) who were receiving ethambutol (20 mg/kg/day for 12 months) as part of their antituberculosis treatment had their visual evoked responses (VER) recorded. VER, which gauges visual acuity, has the capacity to spot consequences of subclinical ocular toxicity. At months 0, 2, 3, 6, and 12 of treatment, as well as between three and six months after the drug was stopped, VER exams were conducted. The authors of this study came to the conclusion that VER measurement should be used routinely for paediatric tuberculosis chemotherapy because there was no significant change in it at any point during the study.

In two additional studies conducted in India,[16,17] 16 and 54 children with tuberculosis between the ages of 2 and 14 years old, respectively, received ethambutol treatment (25 mg/kg/day for two to three months, followed by 15 mg/kg/day for four to nine months), and ophthalmological examinations were carried out. When ethambutol was halted for 4 months and then restarted, there was no return of the oedema in the one case[17] with minor optic disc oedema after 7 months in an 11-year-old child without visual complaints.

In Korea, 45 tuberculosis children between the ages of 1 and 15 were given isoniazid and ethambutol (15–25 mg/kg/day) for 9–18 months. Each month, all patients underwent assessments that included testing for visual acuity, colour vision, macular thresholds, and visual fields. Ethambutol's eye toxicity was not detected in any of the patient evaluations (unpublished data from the MRC working party on TB of the spine; personal communication from Wallace Fox*).

30 children in Romania[19] between the ages of 4 and 5 underwent intermittent ethambutol (25 mg/kg) treatment for tuberculosis (2 days a week). At months

0, 3, and 6 of treatment, they underwent ophthalmological examinations that included assessments of their visual acuity, visual field, chromatic sense, pupillary reflexes, and fundus. Ocular toxicity was not reported in any cases.

[In a trial conducted in Great Britain,[20] 151 kids aged 0 to 14 were given ethambutol for 2 to 9 months (14% for more than 6 months — 22% received less than 13 mg/kg and 30% more than l7 mg/kg; 12% received more than 17 mg/kg for more than 2 months). Two years after the completion of treatment, all were tracked down; just one suspected case of eye harm was reported, but no ophthalmological examination was done.

Studies that don't specifically follow up with ophthalmologists

Ethambutol has been successfully used in India to treat paediatric tuberculosis. [16,17,21,22]. The dosage used was typically 25 mg/kg for two to three months, then 15 mg/kg for nine to ten months. No ocular side-effects were noted among the 219 kids who were included in the last two articles mentioned, ranging in age from 2 months to 18 years. Ethambutol was used during the second phase of treatment for 10 months at a dosage of 17.5 mg/kg/day in a different study of tuberculous meningitis[23] in 180 children aged 0 to 10 years; no visual problems were associated with the use of ethambutol. When ethambutol was administered to youngsters in Spain,[24] no ocular side effects were noted.

Official Recommendations

Although it is believed that, generally, the findings in adults apply to children, there is limited evidence on the outcomes of short-term tuberculosis treatment in children. Ethambutol is often very well tolerated in adults and is virtually always suggested for at least the first two months of treatment. [25 - 27]

Due to the limited ability of young children to self-report eye problems, its usage is typically not advised:

- "Ethambutol is best avoided in children too young for objective eye tests, and also in adults with language or communication problems", according to a report of the Joint Tuberculosis Committee of the British Thoracic Society,[9] 1986.
- "In children who are too young for assessment of visual acuity, and red-green colour discrimination (generally under age 6), ethambutol should be used with particular caution and after consideration of possible alternative drugs," advised by the World Health Organization in 1991[26] and the American Thoracic Society and the Centres for Disease Control,[27] in 1994.
- The International Union Against Tuberculosis and Lung Disease's Tuberculosis Guide:[25] The current fourth edition does not specifically address the risk of ethambutol in children; nevertheless, the second edition stated that children should never use ethambutol.

DISCUSSION:

In accordance with national tuberculosis control programmes, the use of ethambutol is advised during the intensive phase of tuberculosis treatment for sputum-positive cases of pulmonary tuberculosis as well as during the consolidation phase of treatment for all tuberculosis types if thioacetazone is not prescribed or if the treatment with rifampicin cannot be closely monitored.[25, 27] However, because to its reported ocular toxicity, most practitioners in many nations are hesitant to use ethambutol for children.

There have been relatively few reports of major ocular complications in children treated with ethambutol, and all of the data gathered here demonstrate an excellent level of medication tolerance. The authors (from the British MRC) came to the conclusion that ethambutol might be administered even in young children in the one study where a suspected instance of ocular toxicity was reported among children.[20] This review reveals no specific issues with children, and those able to collaborate with the carers, typically older children and adults, should utilise it with the same caution as adults.

The way ocular side-effects are assessed in those under the age of 5 or unable to communicate clearly is very imprecise according to the authors of the literature. While the visual evoked response test provides a measurement independent of the child's conscious participation, this is not the case for clinically tested visual acuity, colour vision, or visual field. Furthermore, when ethambutol is administered at a dose of 15 mg/kg/day, ocular adverse effects are incredibly uncommon. It seems reasonable to recommend the use of ethambutol without excessive concern for side effects, even among very young patients, if it is estimated that it should be included in the standardised regimen for any reason (high level of resistance, directly observed treatment with rifampicin impossible to manage, rifampicin not included in the standardised regimen, difficulties in drug supply, etc.).

CONCLUSION:

Ethambutol can be administered routinely to children 5 years of age and older at a dose of 15 mg/kg/day without adding any additional safety measures, and this should be included in official recommendations. Ethambutol can also be administered to younger children without needless concern for adverse effects.

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