Ethambutol: The Turtle of the Fifty Year Race!

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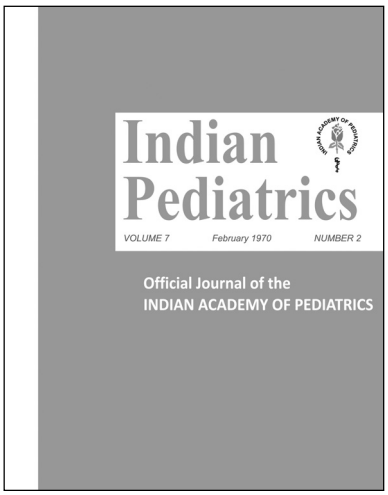
As we come closer to achieve the Sustainable development goal of ending tuberculosis (TB) by 2030 [1], it is time to relook on the journey of one of the earliest discovered and effective anti-tubercular drug with a low potential for resistance – Ethambutol. This bacteriostatic drug was discovered in 1961 at the time when the then triple therapy (isoniazid, streptomycin, para-amino salicylic acid) was starting to get overpowered by resistant organisms, rising incidence of TB, and multiple side-effects [2,3].



PAST

Almost fifty years back, Patwardhan, *et al.* [2] concluded that ethambutol-isoniazid (INH) combination was effective in treatment of primary childhood TB [2]. This conclusion was based their study on 60 children, 6 months to 5 years age, diagnosed with primary tuberculosis. The study compared three regimens: INH alone; streptomycin-INH combination; and ethambutol-INH combination. INH was dosed at 15-20 mg/kg in two divided doses whereas ethambutol was started at 25mg/kg, later reduced to 15 mg/kg as symptoms improved. Both the drugs were given for a period of one year. Streptomycin was given at 40-50 mg/kg intramuscular daily for 6 weeks followed by alternate day for next 6 weeks. Children were then followed upto 2 years. Significant clinical improvement was noted in all three groups, maximum being in streptomycin-INH group. Radiological clearing was earliest in the ethambutol-INH group. Recurrence was noted more often in children receiving INH alone or those receiving ethambutol-INH when the dose of ethambutol was decreased to 15 mg/kg. At that time INH alone was widely used and resistance rates had started rising; rates were reported to be 16% in primary cases and almost 49% in previously treated cases [2]. Streptomycin resistance was also high – varying from 14% in primary cases to 46% in secondary cases.

On the other hand, ethambutol was a less used, newer drug showing comparable efficacy, ease of oral administration and low rates of resistance. In the same year, another study in the journal by Mankodi, *et al*. [3] concluded that ethambutol is an effective bacteriostatic drug to be used as an adjuvant to INH in children who were poor responders or had failed triple drug standard therapy. The study included 16 children diagnosed with TB but unresponsive to streptomycin, INH or para-amino salicylic acid (PAS). These children were treated with ethambutol-INH combination for 8-18 months. Ethambutol was given as 25 mg/kg daily for 3 months and then 15 mg/kg daily for rest of the therapy duration along with INH at 20 mg/kg daily. Almost 80% of the cases (13/16) showed good response. Most children showed clinical improvement in first six months. Adverse effects, noted to be disc edema and thyroid enlargement, were minimal and reversible.

PRESENT

Fifty years later, ethambutol continues to be one of the standard drugs in TB management, now given in combination with INH, rifampicin and pyrazinamide. With the latest guidelines, the drug is now part of both intensive phase and continuation phase of treatment [4,5] . The most significant side effects that need clinical monitoring are optic neuritis and altered color vision. Pre-treatment check and immediate cessation of drug at onset of symptoms remains the key. Ethambutol has a clear dose-related efficacy and toxicity as a result of which appropriate dosing has always been a topic for research. In the last fifty years, many more studies were conducted. In a major study from India published in 1991, Seth, *et al*. [6] studied the visual evoked responses (VER) of children between 3-13 years who were treated with ethambutol at 20 mg/kg given for tuberculosis. They could not find any

greater risk of ethambutol induced optic damage as compared to adults. In another review by Graham, *et al.*[7] in 1998, more than fifteen studies were analyzed for ethambutol toxicity in children. They once again concluded that the risk associated with ethambutol is minimal if given in appropriate doses. Serum concentrations of ethambutol in children have been reported to be lesser than adults when given at the same dose [7,8]. Finally, World Health Organization in 2006 [9] reviewed all the published literature on dosage, toxicity and pharmacokinetics in which they found that ethambutol in combination with INH shows better response when given at 25 mg/kg as compared to 15 mg/kg suggesting a dose-related efficacy [10]. They also found that ocular toxicity was again dose-related and occurred mostly above 50 mg/kg in adults. The pharmacokinetics of the drug showed that the peak serum ethambutol levels in children at the same dose were lesser than adults making them less susceptible to side-effects. Considering all the above facts, they standardized the daily dose of ethambutol in children to 20 mg/kg (range 15-25 mg/kg). Another Indian study published in 2016 [11] suggested that the two hour serum levels of ethambutol were low in more than 50% of the study population at a mean dose of 21.7 mg/kg further putting in doubt if a still higher dose is actually needed.

The drug is also valued for the protection it offers to other companion drugs against development of drug resistance. In the first national anti TB drug resistance survey in 2016 [12], primary and secondary TB cases showed highest resistance to INH and lowest to ethambutol (primary cases: INH-11.1%, pyrazinamide-6.9%, streptomycin-6.9%, ethambutol-2.3%; secondary cases: INH-25.1%, pyrazinamide-8.8%, streptomycin-13.3%, ethambutol-7.0%). In the same survey, resistance to ethambutol in MDR-TB was 46.98%. As per the RNTCP updated pediatric guidelines for drug resistant TB, the drug continues to be used in intensive and continuation phase of mono/poly - drug resistant TB, shorter MDR-TB regime and MDR/RR TB without additional resistance to fluroquinolones and/or second line injectable drugs [5]. For the conventional long MDR TB regime, it is now placed in category C; used as an add-on drug. With the latest WHO 2019 update on drug resistant TB, the drug continues to be part of complete therapy for INH resistant TB and as one of the add on drugs for MDR TB[13].

CONCLUSION

As we move from Revised National Tuberculosis Control Program (RNTCP) to National Tuberculosis Elimination Program (NTEP), ethambutol has come a long way. To start as drug of choice in cases resistant to then TB drugs few decades back, it still continues to be one of the drugs in MDR-TB besides being an essential drug for complete regimen in non-resistant cases.

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