Ethambutol in tuberculosis: time to reconsider?

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In the wake of the worsening tuberculosis (TB) situation in young African adults, the number of clinically diagnosed cases of childhood TB is also steadily increasing.¹ The recent and proposed introduction into Malawi of new anti-TB regimens, which include ethambutol has prompted us to reconsider the safety of using this drug in young children.

Revision of treatment regimens in Malawi

Table 1 shows the regimens used in Malawi for new cases of TB. Having used thiacetazone for approximately 12 years, the Malawi National TB Programme removed it from its essential drug list in January 1997 and substituted ethambutol. Most paediatric cases of TB fall into the category of smear negative pulmonary TB. The proposed new regimen consists of a two month initial phase (with the first two weeks spent in hospital) of supervised rifampicin, isoniazid, and pyrazinamide given three times a week, followed by a six month continuation phase of daily unsupervised isoniazid and ethambutol. For those children with smear positive pulmonary TB and serious forms of extrapulmonary TB, ethambutol is added to the two month initial supervised phase of treatment. Patients with TB meningitis are an exception to the proposed changes and will continue to be given the current regimen.

Reasons for change and potential risks

From the viewpoint of TB management in Malawi, the advantages of these changes are as follows.

- (1) The risk of nosocomial transmission of human immunodeficiency virus (HIV) and hepatitis B associated with the use of intramuscular streptomycin in overcrowded wards and those with poor resources is removed.
- (2) The danger of thiacetazone induced cutaneous reactions in HIV positive patients is removed.
- (3) The duration of hospital admission which accompanied the initial phase is decreased from two months (for injections) to around two weeks, the time required for patient education.
- (4) The cost of treatment is reduced as the overall cost of intramuscular injections (drugs, syringes, needles, water for injections, sterilisation) exceeds that of ethambutol.²
- (5) The staff time needed for the preparation and administration of intramuscular injections is reduced.

These advantages apply in treating TB in adults and children. There is also the added attraction of using the same regimen for all

patients, regardless of their disease status or age, and this simplicity improves the understanding of TB treatment by health care staff and the likelihood of patient compliance. A major concern for TB control is treatment compliance and potential risks include the following.

- (1) A poor understanding of and poorer compliance with drugs due to a shorter period of hospital supervision.
- (2) The perception of losing, without the injections, a "leash" to ensure patient adherence to treatment.
- (3) The sale of anti-TB drugs, particularly rifampicin, in the local market.
- (4) The possibility of ethambutol toxicity.

Ethambutol toxicity

The major side effect of ethambutol is retrobulbar optic neuritis of two types: axial and periaxial. The most common form is associated with macular degeneration, decreased visual acuity, and decreased colour perception. The periaxial type is associated with visual field defects. The mechanism is unclear. Toxicity is generally dose related, becomes evident three to six months after starting the drug, and is often reversible on stopping treatment with the drug. If the diagnosis is delayed, however, as it may be if symptoms are not reported, visual damage may be permanent.^{3,4}

The recommended dose for adults, irrespective of the stage of treatment, is 15 mg/kg/day or 30 mg/kg three times a week.⁵ Early reports of ethambutol in adults found toxicity to be a dose related phenomenon. A single daily dose of between 60 and 100 mg/kg caused optical toxicity in eight (44%) of 18 patients.⁶ Liebold reported a 19% incidence of ocular toxicity among 59 patients receiving dosages of over 35 mg/kg compared with 3% (two patients) among 59 receiving doses of less than 30 mg/kg.³ Studies using doses ranging from 15 to 25 mg/kg have reported complications in 1-3% of adults.⁷⁻¹⁰ Thus reported cases are usually related to high doses and the risk of optical neuritis at 15 mg/kg/day is now considered to be negligible. An idiosyncratic reaction has been reported in a patient who developed rapid irreversible blindness within a week of starting treatment at that dose.¹¹

Ethambutol doses in children

There is a concern that toxicity may develop in children too young to report early visual symptoms. Understandably, reviews of anti-TB chemotherapy in children, consensus statements, and World Health Organisation (WHO) directives advise against the use of ethambutol in young children.¹²⁻¹⁴ This position has been cautiously revised in response to the appear-

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Table 1 Treatment regimens in Malawi for new cases of tuberculosis

Indicators	Regimens		
	Past 1984–96	Current 1997–	Proposed
Smear positive pulmonary tuberculosis			
Pericardial tuberculosis			
Miliary tuberculosis			
Spinal tuberculosis	2SRHZ/6TH	2SRHZ/6EH	2R _h H ₂ Z _h E _h /6EH
Tuberculosis meningitis	2SRHZ/7RH2	SRHZ/7RH	2SRHZ/7RH
Smear negative pulmonary tuberculosis	1SSTH/11TH	1SEH/11EH	2R _h H ₂ Z _h /6EH
Other extrapulmonary tuberculosis not mentioned above			

Regimens are divided into intensive phase and continuation phase. The number before the first letter of each phase of the regimen is the duration in months of that phase. The numbers in subscript after the name of the drug indicate the number of times the drug should be taken in a week.

S, streptomycin; R, rifampicin; H, isoniazid; Z, pyrazinamide; T, thiacetazone; E, ethambutol.

ance of drug resistant strains.¹⁵ In fact, a more recent review concludes that “it seems reasonable to recommend the use of ethambutol without undue fear of side effects, even among very young patients”, though the author stops short of specifying doses for children less than 5 years old.¹⁶

Pharmacokinetic data in children from Germany show that ethambutol doses need to be higher than in adults to achieve the desired minimum inhibitory concentrations.^{17, 18} These workers recommend a daily dose of 25 mg/kg for children less than 7 years old, 20 mg/kg for children aged 7–11 years, and 15 mg/kg for those older than 11 years. No case of toxicity was found in the use of such a schedule in 2634 German children aged 3–14 years, although methods of evaluation for visual toxicity were not specified.¹⁹ Additional pharmacokinetic studies are needed to confirm the current recommended dosage schedules for anti-TB drugs in children as the data are often extrapolated from experience in adults.²⁰

Ethambutol toxicity in children

We have no experience in using ethambutol in children, so we have reviewed the available published work. Although ethambutol has been used in many countries and continues to be used in young children, we have not been able to find a single report of confirmed visual toxicity related to this use (tables 2 and 3), except perhaps in the context of TB meningitis. A report from Thailand reported optic atrophy in six of nine children with TB meningitis treated with ethambutol, compared with only two of nine children who did not receive ethambutol.²¹

Table 2 lists those studies that have specifically sought evidence of optic neuritis. Visual evoked cortical responses and colour discrimination are confirmed means of detecting subclinical side effects.^{22, 23} A study from India

followed 47 children, including 27 aged less than 5 years old, receiving 20 mg/kg/day ethambutol for 12 months and found no effect on visual evoked responses during treatment or up to three to six months after stopping treatment.²⁴ A study from Mexico followed 36 children for four years, 21 of whom were infants. Testing for visual acuity, fields, and colour perception was performed every three months until the completion of treatment and no evidence of optic toxicity was found.²⁵

A study comparing different regimens for spinal TB in Korea included children less than 5 years of age and found no evidence of toxicity on monthly assessment using similar evaluation methods (unpublished data from Medical Research Council working party on tuberculosis of the spine, personal communication from Fox W quoted in *Tubercle* 1986;67:27). Infants and young children are an age group in which the clinical diagnosis of TB in Malawi is common. Follow up studies from Thailand, Germany, and Romania have also found no evidence of toxicity.^{26–28}

Many other studies report the use of ethambutol in young children with no apparent problem, though specific follow up evaluating for evidence of optical toxicity is not clearly outlined in the reports.^{18, 19, 29–36} Table 3 summarises these reports. The doses used range from 15 to 30 mg/kg/day for periods of two to 14 months. These reports included a large number of young children less than 5 years of age. The Medical Research Council (UK) reported that ethambutol was a part of the chemotherapy used in the treatment of 151 children with TB, nearly a third of whom were less than 5 years of age, with doses up to 30 mg/kg. Thirty per cent of these children received ethambutol in the initial phase and “one possible non-confirmed case of ocular toxicity” is mentioned.²⁹ One study compared

Table 2 Studies that have specifically sought optical toxicity

Reference	Patients (n)	Age range	Method of evaluation	Dose of ethambutol (mg/kg/day)	Duration of treatment (months)	Length of follow up (months)	Number with toxicity
24	47	3–13 years	Visual evoked responses	20	12	15–18	0
25	36	4 months to 16 years	Acuity/field/colour	25 then 15	6 then 18	24–48	0
Fox*	45	1–15 years	Acuity/field/colour	15–25	9–18	9–18	0
26	30	4–5 years	Acuity/field/colour	25 twice a week	6	6	0
27	27	5–15 years	Acuity/field/colour	20	2–24	12–36	0
28	6	9–16 years	Computerised visual field examination	20	12	9	0

*Fox W, unpublished data quoted in *Tubercle* 1986;67:27.

three regimens for TB meningitis. Whether any of the visual sequelae among survivors could be attributed to ethambutol usage rather than the TB meningitis could not be ascertained as all the groups received the same dose of ethambutol.³⁶

The possibility of fetal toxicity must also be considered. Regimens that include ethambutol are recommended for use in pregnancy.³⁷ One case report that measured ethambutol concentrations in amniotic fluid, maternal, placental, and cord blood specimens suggests that the placenta is not a significant physiological barrier to the transfer of ethambutol to the fetus.³⁸ We have found two reports of ocular malformations in newborn infants of mothers receiving ethambutol in the first trimester.^{39, 40}

Published work suggests that the risk associated with ethambutol in children is minimal as long as appropriate dosages are used. In the light of the report from Thailand,²¹ and because ethambutol may more easily cross the blood-brain barrier if the meninges are inflamed, it would seem prudent to continue with the current recommended regimen (2SRHZ/7RH) for patients with TB meningitis.

Childhood TB and the advantages of ethambutol in Malawi

In Africa, the incidence of TB in children aged 0–14 years is predicted to increase from 42/100 000 in 1990 to 447/100 000 in the year 2000.⁴¹ In the Blantyre district in Malawi, the number of children treated for TB in the 0–14 year age group has increased from 64 in 1986 to 507 (or 19% of all registered cases) in 1995. It is worth noting that the number of extrapulmonary and miliary cases has also proportionately increased from 13 to 89 over the same period, remaining at around 20% of all childhood cases.⁴² Given the difficulties in confirming a diagnosis of pulmonary TB in children, the number of extrapulmonary cases may be a better indicator of the real trend.⁴³ This increase is largely as a result of HIV infection and a resurgence of TB in the young adult population.

Most Malawian children with a diagnosis of TB are classified as smear negative pulmonary TB and thus would receive ethambutol in the second phase of treatment only at a dose of around 15 mg/kg/day. Our review suggests that such a regimen is associated with negligible risk. It is important to note that follow up evaluation for possible optical toxicity is not an

Key messages

- Ethambutol toxicity is generally dose related
- There is no confirmed report of ethambutol toxicity in children, except perhaps in TB meningitis
- In the context of co-infection with HIV in African children, there are significant advantages to ethambutol usage over thiacetazone and streptomycin
- Uncertainties include appropriate dosage schedules and whether malnutrition may increase the risk of toxicity

option on a national level. The dose for those smear positive and extrapulmonary cases who would be treated with ethambutol in the initial phase would be around 30 mg/kg three times a week. As smear positive pulmonary TB occurs only in older children, it would be the young children with extrapulmonary TB, excluding TB meningitis, who would be most at risk from ethambutol due to their inability to report early visual side effects. This group accounts for less than 20% of the total case load.

There are considerable advantages to using these new regimens (2R₃H₃Z₃E₃/6EH and 2R₃H₃Z₃/6EH; see table 1) in childhood TB in resource poor countries such as Malawi, particularly in the context of the HIV epidemic. As already mentioned, these largely relate to the exclusion of thiacetazone and streptomycin. Severe reactions to thiacetazone are significantly more common in HIV positive children⁴⁴ and its ongoing inclusion in our national TB programme would be difficult to justify.⁴⁵ An alternative effective regimen for children may be proposed similar to that for TB meningitis (2SRHZ/7RH). There are disadvantages of using a rifampicin based regimen throughout treatment, however, because of expense, a lack of ability to provide supervision for every dose of rifampicin, and the demand for this drug on the black market in Malawi. Of course, these are not concerns for countries such as the UK where rifampicin is often used through the whole treatment course.

The strong epidemiological link with HIV means that children with a clinical diagnosis of TB not only have a high incidence of HIV infection themselves, but that their parents are also likely to be HIV positive, to be ill, or to

Table 3 Studies where occurrence of side effects is mentioned but method of evaluation is not outlined

Reference	Patients (n)	Age range (years)	Dosage of ethambutol (mg/kg/day)	Duration of treatment (months)	Side effects
19	2634	3–14	15–25	Not stated	None
18	26	3–14	15–25	Not stated	None
30	151	1–14 (45 < 5)		2–9	1 case with possible ocular toxicity; not confirmed
31	105	0–5	25 for 2 months then 15	3–12	None
32	104	0–18	15	12–14	None
33	11	2–13	15–25	2	None
34	34	0–10	25 for 2 months then 15	12	Minimal oedema of optic disc without visual symptoms
35	16	3–12	25 for 3 months then 15	12	None
36	54	1–14	25 for 2 months then 15	6	None
37	180	0–10 (136 < 5)	17	10	None

have recently died. In this tragic social setting, prolonged inpatient treatment for streptomycin injections can be difficult, and home management is often more appropriate.

HIV/TB infection and ethambutol

The association of HIV infection with TB in African children is uncertain. Owing to the difficulty in making a diagnosis of pulmonary TB, even in non-HIV infected young children,⁴⁶ the exact incidence of co-infection remains unclear. Evidence from necropsy studies does not support a strong association.⁴⁷⁻⁴⁸ Studies that rely more on a clinical diagnosis find a strong link.⁴⁴⁻⁴⁹ We found a 63% HIV seropositivity among 159 children tested on our paediatric TB ward between October 1995 and September 1996.⁵⁰ An earlier outpatient study in our TB contact clinic found an HIV seropositivity of 18% among 180 children with a diagnosis of TB.⁵¹ Although some of these cases are almost certainly not TB, the patients are diagnosed and treated as such. There are no available data on whether HIV infection might increase the risk of ethambutol toxicity.

Malnutrition and ethambutol

Other uncertainties remain. Studies of isoniazid show that faster metabolism occurs in younger children and higher doses are well tolerated. The available data on ethambutol suggest a similar picture. On the other hand, malnutrition may be associated with a longer serum half life and bioavailability, as with isoniazid and rifampicin.⁵² Our audit found that half the children treated with the more intensive regimen are marasmic (less than 60% weight for age) on admission,⁵⁰ though this inpatient study represented the more severe spectrum of presentation.

Although the mechanism of optical toxicity is unknown, ethambutol is a known chelator of zinc and it has been suggested that zinc deficiency may increase the risk of toxicity.⁵³⁻⁵⁴ Zinc deficiency is likely to be common among Malawian children because of the high phytate content of the maize based diet.⁵⁵

Outstanding questions

As childhood TB is usually not infectious and there are the often acknowledged difficulties in making a definitive diagnosis in resource poor countries, paediatric TB is not given the same priority in national control programmes or research as adult disease. The tendency, therefore, is to fall in line with the adult regimens when the magnitude of the problem is such that the public health perspective of optimising control might take priority over individual management.

By doing this in Malawi, the following three major questions remain.

- (1) What is the minimum dose for infants and young children that is effective?
- (2) To what extent do protein-energy malnutrition, zinc deficiency, and HIV infection affect absorption metabolism, treatment response, and the risk of toxicity?
- (3) Does the inclusion of ethambutol confer any therapeutic advantage?

Until these questions are answered, we remain conservative in our dose for young children at 15–20 mg/kg/day or 25–35 mg/kg three times a week, perhaps sacrificing a degree of therapeutic effectiveness for a margin of safety.

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