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REVIEW ARTICLE

Ethambutol dosage for the treatment of children: literature review and recommendations

P. R. Donald,* D. Maher,† J. S. Maritz,‡ S. Qazi§

*** Department of Paediatrics and Child Health, Faculty of Health Sciences, Stellenbosch University, Tygerberg, South Africa; † Stop TB Department, World Health Organization, Geneva, Switzerland; ‡ Biostatistics Unit, Medical Research Council of South Africa, Tygerberg, South Africa; § Department of Child and Adolescent Health and Development, World Health Organization, Geneva, Switzerland**

SUMMARY

The currently recommended daily dose of ethambutol (EMB) for the treatment of tuberculosis (TB) in children varies from a maximum daily dose of 15 mg/kg body weight daily (without a range) to 15–20 mg/kg and 20 mg/kg (range 15–25 mg/kg). Published evidence relating to the dosage, toxicity and pharmacokinetics of EMB in children and adults is reviewed and a dose of EMB for use in childhood is recommended. Using key words 'ethambutol', 'childhood', 'TB', 'pharmacokinetics', 'bioavailability' and 'toxicity', Medline searches were conducted; cross-references were sought from original papers, books and conference proceedings dating from 1961. When English summaries were available, data were extracted from papers in languages other than English.

EMB has a dose-related efficacy best seen when given to adults alone or with a single other drug. Together with isoniazid (INH), a dose of 15 mg/kg EMB gave better results than 6 mg/kg, and 25 mg/kg better than 15 mg/kg. The occurrence of ocular toxicity was also dose-related; >40% of adults developed toxicity at doses of >50 mg/kg, and 0–3% at a dose of 15 mg/kg/daily. Peak serum EMB concentrations increase in relation to dose, but are significantly lower in children receiving the same dosage. In only 2 of 3811 children (0.05%) receiving EMB doses of 15–30 mg/kg was EMB stopped due to possible ocular toxicity; children of all ages can be given EMB in daily doses of 20 mg/kg (range 15–25 mg/kg) and three times weekly intermittent doses of 30 mg/kg body weight without undue concern.

KEY WORDS: ethambutol; toxicity; dosage; tuberculosis; childhood

> Enough has been said to suggest that ethambutol is no competitor for isoniazid, but it might well be considered a companion drug and replacement for PAS. Two factors will determine this: cost and side reactions.
> —Aaron Chaves, 1966[1]

IN 1961, the Lederle Company announced the discovery of a new anti-tuberculosis agent.[2] 'In the course of screening randomly selected synthetic compounds, N,N'-diisopropylethylenediamine was found to protect mice from otherwise lethal infection with *Mycobacterium tuberculosis*, strain H37Rv.' In vitro concentrations of 1–4 μg/ml inhibited growth of *M. tuberculosis* H37Rv; the new agent, ethambutol (EMB), was also shown to be effective in tuberculosis (TB) infected guinea pigs.[3] Unfortunately, it was soon apparent that this promising agent was responsible for 'toxic amblyopia', which developed in 8 of 18 patients (44%) receiving 60–100 mg/kg body weight/day of EMB.[4] It was, however, noted that the 'ocular disturbances improved on cessation of the drug'.

More than 40 years later, EMB is established as a first-line anti-tuberculosis agent valued for the protection offered to companion drugs against the development and consequences of drug resistance. Its use in adults is usually accompanied by the admonition that 'patients should be advised to discontinue treatment immediately and to report to a clinician if their sight or perception of colour deteriorates'.[5] Because of this serious complication there has been considerable reluctance to use EMB in young children, and most guidelines recommend that EMB should not be given to children younger than 5 or 7 years of age. Nevertheless, there is a considerable body of literature attesting to

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Correspondence to: P R Donald, Department of Paediatrics and Child Health, Faculty of Health Sciences, Stellenbosch University, P O Box 19063, Tygerberg 7505, South Africa. Tel: (+27) 21 938 9592. Fax: (+27) 21 938 9138. e-mail: prd@sun.ac.za

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the use of EMB in young children; in only 2 of 3811 cases (0.05%) was EMB stopped due to fears about poorly documented ocular toxicity.[6,7]

What is indisputable is that there is a desperate need in high TB burden countries for an oral drug such as EMB with a low toxicity. The problem is that the most serious complication of EMB is impossible to detect satisfactorily in young children. This is particularly true in resource-limited developing countries, where the need is greatest. In the presence of an escalating human immunodeficiency virus/acquired immunedeficiency syndrome (HIV/AIDS) epidemic, injections, as needed with streptomycin (SM), are inadvisable, and thioacetazone has fallen into disrepute because of frequent toxic hypersensitivity reactions. If Category I treatment is needed there is little alternative to EMB. The only decision to be made is what dosage should be used, and whether its use should be restricted to children aged >7 years.

From the national TB control programme (NTP) perspective, most children have sputum, or gastric aspirate, smear-negative, paucibacillary forms of primary TB and can be successfully treated with a Category III regimen consisting of isoniazid (INH), rifampicin (RMP) and pyrazinamide (PZA) in the initial phase. The number of children with serious forms of TB needing Category I treatment (four drugs, namely INH, RMP, PZA and EMB in the intensive phase) is relatively small. EMB is therefore reserved for the minority of children who have more extensive disease requiring Category I treatment and for children with drug-resistant TB, where the risks attached to the use of EMB can be better justified. Despite its greater efficacy there are also problems with reliance upon RMP, rather than EMB, in the continuation phase in developing countries. These include its extra expense, the necessity to supervise treatment and the risk that the drug might be sold on the black market.[7]

In addition, current recommendations for the dose of EMB in children are not uniform. World Health Organization (WHO) recommendations vary from advice not to use EMB in children aged <5 years[8] to 15 mg/kg (without a range)[5] and 20 mg/kg (range 15–25 mg/kg).[9]

In the present document, published evidence relating to the dosage, toxicity and pharmacokinetics of EMB is reviewed and a dosage is recommended for use in children.

METHODS

Using the key words 'ethambutol', 'childhood', 'tuberculosis', 'pharmacokinetics', 'bioavailability' and 'toxicity', searches were conducted using Medline. In addition, cross-references were sought from original papers, books and conference proceedings dating from 1961. Data were extracted from papers in languages other than English when English summaries were available.

Fragmentary information relating to children is also available in some 'adult' papers,[10] but the children are often insufficiently identified regarding age and results to provide useful information. In many early articles no attempt at a statistical interpretation of results was made, and authors were satisfied to document 'reversal of infectiousness'. In reviewing data relating to efficacy in adults, particular attention has been paid to the period before approximately 1970. During this period, EMB was often given to drug-resistant patients either alone or in the company of relatively weak drugs; a dose-related effect is thus easier to discern.

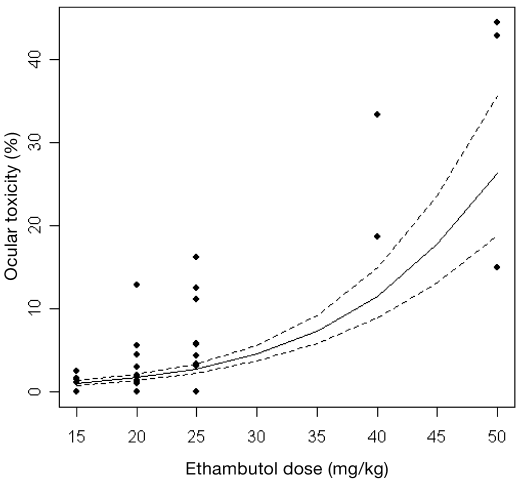

Figure 1 Ocular toxicity (%) and EMB dose (mg/kg). Y = exp (−6.0599 + 0.1006*dose)/(1+ exp[−6.0599 + 0.1006*dose]). Broken lines = 95%CI limits. Data used in Figure 1 are derived from papers listed in Table 1. EMB = ethambutol; CI = confidence interval.

Figure 1 was derived using data from Table 1 where dose levels, the number of patients exposed and the number developing toxicity are recorded. Curve fitting was by logistic regression, the underlying model being a straight line relation between the logit of the probability of toxicity and dose. The lines in Figure 2 were fitted by least squares with weights equal to the numbers of subjects reported in Tables 2 and 3.

RESULTS

The efficacy of ethambutol in adults

Soon after its discovery, the clinical value of EMB was demonstrated in clinical trials in drug-resistant patients and in new 'initial' cases. In drug-resistant patients, it was used both as a sole agent, in otherwise therapeutically destitute patients, and with other second-line agents. In these studies, very high doses of EMB were used, for example 50 mg/kg/ daily[12] or later 25 mg/kg throughout, a dose that was later further reduced to 25 mg/kg for the first 2 months and thereafter 15 mg/kg/daily.[11] With this latter reduction it was hoped to avoid ocular toxicity, while maintaining clinical efficacy. Experience has, however, shown that no clinically effective dose in adults is totally free from the

Table 1 Incidence of optic neuritis following use of EMB in adults in daily regimens (dosages in mg/kg)

Authors	⩽15 *n/N* (%)	15–20 *n/N* (%)	20 *n/N* (%)	20–30 *n/N* (%)	25/15 *n/N* (%)	25 *n/N* (%)	35–50 *n/N* (%)	⩾50 *n/N* (%)
Carr & Henkind (1962)[4]								8/18 (44)
Bobrowitz & Gokulanathan (1965)[11]					0/117	2/18 (11)		
Kass (1965)[12]								9/60 (15)
Place et al. (1966)[13]	0/4					2/16 (13)		3/7 (43)
Corpe & Blalock (1966)[14]						0/118		
Pyle (1966)[15]				4/130 (3)			2/6 (33)	
Donomae & Yamamoto (1966)[16]	0/46		1/49 (2)			2/46 (4)		
Leibold (1966)[17]				2/59 (3)			11/59 (19)	
Ferebee et al. (1966)[18]	4/271 (2)							
Bobrowitz (1966)[19]	1/85 (1)				1/89 (1)			
Bobrowitz & Robins (1967)[20]								
Tai & Chen (1968)[21]					1/100 (1)			
Adel (1969)[22]					10/78 (13)*			
Citron (1969)[23]						2/34 (6)		
Horsfall (1969)[24]					3/68 (4)			
Radenbach (1969)[25]					6/300 (2)			
Wäre (1969)[26]					2/113 (2)			
Pilheu (1970)[10]					0/145			
Roussos & Tsolkas (1970)[27]	4/250 (2)							
Schütz (1970)[28]					0/31			
Tiburtius (1970)[29]					9/300 (3)			
Lees et al. (1971)[30]					1/72 (1)			
Acquinas et al. (1972)[31]					2/36 (6)			
BMRC (1973)[32]	3/118 (3)							
Somner et al. (1973)[33]					0/26			
Barron et al. (1974)[34]					3/304 (3)			
Hong Kong TB Services (1974)[35]					2/107 (2)			
British Thoracic & TB Association (1975)[36]						0/169		
British Thoracic & TB Association (1981)[37]						0/341		
TB Research Centre Madras (1981)[38]	2/120 (2)							
Hong Kong Chest Services/BMRC(1981)[39]					0/239			
DePalma et al. (1989)[40]								
Zn >1 μg/ml						3/53 (6)		
Zn <0.7 μg/ml						5/31 (16)		
TB Research Centre (1997)[41]	0/305							
Jindani et al. (2004)[42]		4/1355 (0.3)						
Griffiths et al. (2005)[43]					8/139 (6)			

* In 6 of these cases, a deterioration in renal function accompanied the development of optic neuritis.
EMB = ethambutol; BMRC = British Medical Research Council; TB = tuberculosis; Zn = zinc.

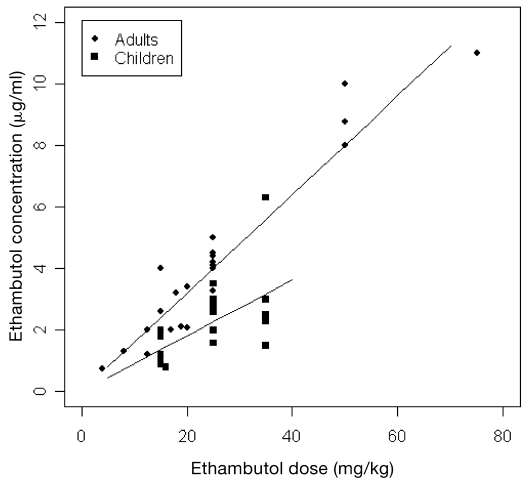

Figure 2 Peak EMB serum concentration (μg/ml) in adults and children. Data used in Figure 2 are derived from papers listed in Tables 2 and 3. The two lines are adults: $y = 0.1602$*dose and children: $y = 0.0906$*dose. The standard errors of the two slope coefficients are 0.005833 and 0.009080, respectively. EMB = ethambutol.

danger of ocular toxicity. At the end of an international conference to discuss EMB, Dr Aaron Chaves, Director of Tuberculosis Clinics for the Department of Health of New York City, stated: 'Enough has been said to suggest that ethambutol is no competitor for isoniazid, but it might well be considered a companion drug and replacement for PAS. Two factors will determine this: cost and side reactions.'[1]

Subsequent events have borne out Dr Chaves' words and, at doses necessitated by the occurrence of optic neuritis, EMB is seen as a bacteriostatic agent. Its main function now is to protect companion drugs against resistance, particularly in the face of INH resistance. How well it fulfils this role at currently recommended doses is a moot point.

In a variety of different liquid and solid media, EMB has an minimum inhibitory concentration (MIC) varying from 0.5 μg/ml to 2.0 μg/ml,[58] from 0.95 μg/ml to 3.8 μg/ml in 7H12 BACTEC broth, and from 1.9 μg/ml to 7.5 μg/ml on 7H10 agar.[59] During in vitro experiments, EMB was less bactericidal than INH, RMP

Table 2 Mean peak serum concentrations (μg/ml) of EMB in relation to dose in adults

Authors	*n*	Dose (mg/kg)	Peak
Place & Thomas (1963)[45]	10	50	10
	10	25	5
	2	17	2
Bobrowitz & Gokulnathan (1965)[11]	64	25	4.1
	46	15	2.6
Peets et al. (1965)[44]	3	25	5
Gómez-Pimienta et al. (1966)[46]	7	20	3.4
Donomae I, Yamamoto (1966)[16]	13	25	4.4
	6	12.5	1.2
Place et al. (1966)[13]	10	4	0.67
	10	8	1.4
	10	12.5	2.0
	10	25	4.0
	10	50	8.5
Horsfall (1969)[24]	25	25	4.1
Eule & Werner (1970)[47]	10	25	4
	10	50	8
	10	75	11
Lee et al. (1977)[48]	6	15	4.01
Israili et al. (1987)[49]			
Day 1	17	12.5	3.7
Days 4–7	17	12.5	5
Kum ar (1992)[50]	4	25	8.2
	4	25	6.4
Schall et al. (1995)[51]	20	7.5*	1.45
Peloquin et al. (1999)[52]			
Fasting	14	25*	4.5
Non-fasting	14	25*	3.8
Zhu et al. (2004)[53]	38	19	2.11
	18	20	2.06
	16	18*	3.21

* Healthy volunteers.
EMB = ethambutol.

Table 3 Mean peak serum concentrations (μg/ml) of EMB in relation to dose in children

Authors	*n*	Dose (mg/kg)	Age, years	Peak
Hussels & Otto (1971)[54]	6	15	2–5	1.2
	6	15	6–9	1.1
	7	15	10–14	0.9
	4	25	2–5	2.0
	7	25	6–9	1.5
	8	25	10–14	2.8
Hussels et al. (1973)[55]	5	35	2–5	1.5
	9	35	6–9	2.3
	14	35	10–14	3.0
	5	35*	2–5	2.5
	9	35*	6–9	2.5
	14	35*	10–14	6.3
Benkert (1974)[56]	4	15	3–6	0.9
	4	15	7–10	2.0
	5	15	11–14	1.8
	5	25	3–6	3.0
	5	25	7–10	2.6
	3	25	11–14	3.5
Zhu et al. (2004)[53]	14	Mean 16	Mean 5.4	0.78
Graham et al. (2006)[57]	18	Mean 33	Mean 5.5	1.8

* Given with RMP 10 mg/kg body weight.
EMB = ethambutol; RMP = rifampicin.

and SM,[60] and did not appear to influence the bactericidal activity of either INH or RMP when given with those drugs either alone or together. At higher concentrations (10 μg/ml) and following longer exposure, much better in vitro bactericidal activity could be demonstrated.[61]

During in vivo experiments with guinea pigs, EMB alone failed to prevent disease progression and did not appear to influence the bactericidal activity of INH or RMP.[62] It was concluded that EMB was unlikely to contribute to the sterilisation of TB lesions, but might assist in preventing drug resistance. Clinical experience has tended to confirm these experimental findings. Other in vitro experiments found that the bactericidal activity of EMB, unlike that of RMP or INH, was not influenced by drug concentrations between 1.25 μg/ml and 5 μg/ml.[63–65] It was considered that the duration of exposure was of more importance at the relevant concentrations than the actual concentration.

EMB given alone to otherwise therapeutically destitute drug-resistant patients led to culture conversion in 36–50% of individuals.[11,16,21,66,67] Failure was often accompanied by the emergence of EMB resistance, thus confirming the activity of the drug. The study of Gyselen et al. provided the best view of future developments when 'reversal of infectiousness' was achieved in 36% of patients receiving EMB alone, 58% of those receiving EMB together with another previously unused drug, but in 83% of those given EMB and the then new agent RMP.[67]

Several early studies compared different doses of EMB (25 mg/kg and then 15 mg/kg vs. 15 mg/kg throughout,[19] 25 mg/kg vs. 12.5 mg/kg[15] and 15 mg/kg vs. 6 mg/kg),[68,69] and provided some evidence of a dose-related effect upon reversal of infectiousness and the prevention of drug resistance. The results of these and other early studies are summarised in Table 4.

Later drug trials increasingly concentrated upon the all-important aspect of sterilisation of lesions reflected in the relapse rate and the ability of agents to support other agents in the regimen by preventing the development of drug resistance or the expansion of existing resistance.

In an assessment of the value of different agents in preventing the emergence of resistance in the companion drug, resistance to INH emerged in 4% of cases when EMB was combined with INH and resistance to RMP in 18% of cases when EMB was combined with RMP.[70] EMB is thus considered to have only a moderate ability to protect companion drugs from resistance.[71] In the presence of INH or SM resistance, EMB has in some studies appeared to contribute to a favourable outcome. Thus, in an evaluation of 6-month and 8-month regimens during which PZA could be compared with EMB, patients in the EMB series had a considerably higher relapse rate after either 6 or 8 months of treatment.[72] However, among patients with strains

Table 4 Efficacy of daily doses (mg/kg body weight) of EMB in adults, 1965–1973

Study	Regimen	EMB dose	Duration of evaluation	Patients	Bacteriological efficacy* *n* (%)
Bobrowitz & Gokulanathan (1965)[11]	EMB with CS/VIO or PZA	25 & 25/15	At least 4 months	28 retreat	21 (75)
	EMB alone	25		15 retreat	2 (13)
Kass (1965)[12]	EMB+CPM with PZA/ETH/CS	50	At least 4 months	24 retreat	24 (100)
Ferebee et al. (1966)[18]	EMB+INH	6	20 weeks	131 initial	122 (93)
Donomae & Yamamoto (1966)[16]	EMB+INH	12.5	6 months	38 initial	30 (79)
	EMB+INH	25	6 months	39 initial	38 (98)
	EMB 1 g daily alone	20	6 months	49 retreat	20 (41)
	EMB 1 g alternate days alone	20	6 months	46 retreat	12 (26)
	EMB & other drugs	25/15	3 months	45 retreat	28 (58)
Pyle et al. (1966)[66]	EMB+INH	20–30	3 months	26 initial	15 (58)
	EMB+INH		6 months	23 initial	23 (100)
	EMB+INH+SM		3 months	55 initial	40 (69)
	EMB+INH+SM		6 months	57 initial	57 (100)
Corpe & Blalock (1966)[14]	EMB+ETH+KM	25	>6 months	118 retreat	83 (70)
Bobrowitz & Robins (1967)[20]	EMB+INH	25/15	>4 months	89 initial	71 (95)
	EMB+INH	15	>4 months	85 initial	54 (89)
	PAS+INH	—	>4 months	74 initial	42 (82)
Gyselen et al. (1968)[67]	EMB alone	25/15	20–121 weeks	14 retreat	5 (36)
	EMB & other drugs	25/15	29–123 weeks	19 retreat	11 (58)
	EMB+RMP	25/15	20–70 weeks	12 retreat	10 (83)
Tai & Chen (1968)[21]	EMB+INH	25/15	1 year	100 retreat	45 (46)
Pilheu (1970)[10]	EMB+INH	25/15	1 year	145 initial	141 (97)
Doster et al. (1973)[69]	EMB+INH	6	20 weeks	91 initial	80 (88)†
		15		114 initial	105 (91)

* Bacteriological efficacy refers to sputum culture negativity.
† Eight of the 11 EMB 6 mg/kg failures, but none of the 9 EMB 15 mg/kg failures, were resistant to INH.
EMB = ethambutol; CS = cycloserine; VIO = viomycin; PZA = pyrazinamide; retreat = retreatment; CPM = capreomycin; ETH = ethionamide; INH = isoniazid; SM = streptomycin; KM=kanamycin; PAS = para-amino salicylic acid; RMP = rifampicin.

resistant to INH or SM, those receiving EMB responded more favourably. These results were confirmed in other studies.[73] It should be noted that during these studies the EMB dose was 25 mg/kg during the intensive daily phase and 45 mg/kg during the intermittent continuation phase. The dosages of EMB now in use in adults (15 mg/kg and 30 mg/kg) are respectively 60% and 67% of these doses.

Studies of the early bactericidal activity (EBA) of EMB at a dose of 25 mg/kg body weight found a substantial EBA of 0.246, comparable to that of RMP, which was 0.187.[74] In a later study, a similar EBA (0.245), also at a dose of 25 mg/kg, was reported.[75] As the EBA reflects the ability of an agent to kill the metabolically active bacilli in the walls of cavities, it might also reflect the capacity of an agent to protect companion drugs against resistance. In this respect it should be noted that the EBA of 15 mg/kg EMB was considerably lower, at 0.05. This dose-related decline in activity, although determined in only three patients, is cause for concern.[74]

In the most recent study to evaluate an EMB-containing regimen, EMB was used at dosages of between 15 and 20 mg/kg/body weight in most patients.[42] After a similar intensive phase of INH, RMP, PZA and EMB, patients received INH and RMP for 4 months, or EMB and INH for 6 months. Disappointingly, although only one (4%) of 23 patients who were resistant to INH at the start of treatment and received the INH and RMP continuation phase relapsed, 11 of the 35 (31%) who received EMB and INH in the continuation phase relapsed, again confirming the poor sterilising action of EMB and its failure to protect the regimen from the consequences of INH resistance.

Available evidence from clinical trials performed in adults therefore confirms that, at the dosages that we are constrained to use as a result of unacceptable levels of toxicity at higher dosages, EMB is indeed, at best, bacteriostatic and has a limited influence on the outcome in adult pulmonary TB (PTB).

Toxicity of EMB in adults

> It is necessary still to emphasise that the administration of potent drugs involves a 'calculated risk' where the presumptive benefit is balanced against the possibility of toxic effects and idiosyncrasies: but to calculate wisely it is necessary to know, as accurately as possible, what the risk may be in kind, degree and frequency; and the special condition which may increase or decrease the chance of injury . . . Full information will serve to protect in both ways: against the unjustified fear as well as against the risk of rashness.
>
> —T Sollman quoted by Kass, 1953[76]

Several groups active during the early clinical assessment of EMB commented upon the difficulties of assessing ocular toxicity.[18,20,69] Even among patients

who were not receiving EMB, changes in visual acuity were often documented. In several trials where the clinicians were blinded as to patient allocation, ocular 'toxicity' was documented amongst control groups. The possibility of toxicity was sufficient to cause careful clinicians to stop the drug. Ferebee et al. referred to this as a 'psychological' hazard![18] Early EMB studies tend to be precise in their description of how toxicity was assessed; by contrast, later studies at times do not specifically mention ocular toxicity or its assessment, or they rely upon patients to present with complaints before a formal optic assessment. Having expressed these reservations it must immediately be stated that there is no doubt that EMB ocular toxicity is dose-related, that the incidence declines as the dose declines, but that it has been encountered in adults at all of the doses in clinical use. Case reports confirm undoubted cases of ocular toxicity occurring at an EMB dose of 15 mg/kg. The data (but not the case reports) are summarised in Table 1. Figure 1 illustrates the percentage of cases developing ocular toxicity in relation to EMB dose.

It is also disturbing that refined assessments by ophthalmologists of patients receiving EMB have documented abnormalities with a greater frequency than following a more superficial clinical evaluation.[40,43,77–80] The importance of these abnormalities is uncertain, as is the potential for zinc deficiency to precipitate EMB ocular toxicity. At least one study found a higher incidence of ocular toxicity among patients with low zinc concentrations.[40] Another study found no difference in the serum concentrations of copper or zinc after 2 months of treatment with 25 mg/kg EMB.[81] Children with TB, particularly those with HIV/AIDS, are very likely to be zinc deficient.[82,83]

Efficacy and toxicity of EMB in children

EMB has been used to treat childhood TB almost as long as it has been used in adults. Its use was often confined to children aged >3 years, because of concern about the risk of ocular toxicity and the difficulty of assessing ocular function in young children. As regards efficacy in children there are few, if any, really satisfactory studies comparing the use of EMB with other drugs. Early papers record the absence of overt toxicity and express satisfaction that a drug is available to replace para-amino salicylic acid (PAS), the use of which was associated with considerable patient resistance and gastro-intestinal discomfort. It is also in the nature of childhood TB that broad clinical criteria, such as weight gain and general well-being, are used to assess treatment success. In adult studies, sputum culture negativity is an indisputable criterion of success. In several studies chest radiograph (CXR) clearing was compared between regimens, but again a statistical comparison was often not made. Many cases of childhood disease are also paucibacillary, which, left untreated, would in a significant proportion of cases recover successfully without intervention, especially in children in the group aged 5–10 years. It is thus difficult to precisely assess the success of the use of EMB in children, and we are left to fall back on the evidence provided by adult studies.

Convincing cases of EMB-induced ocular toxicity have not been reported in children,[6,7] although in two children EMB has been stopped as result of poorly documented eye problems.[84,85] Although many reports document merely that a group of children has received EMB without any evident optic toxicity, other studies have evaluated significant numbers of children receiving EMB at doses varying from 15 to 30 mg/kg body weight using sophisticated laboratory and clinical techniques with negative results.[86–90] In addition, Schmid mentions, almost in passing, that he has treated 2634 children with EMB without any evidence of ocular toxicity.[91] Not too much credence can be given to cases of ocular toxicity in association with tuberculous meningitis, as the disease itself will frequently be responsible for the pathology described.[92,93] Finally, it is of concern that the reason toxicity has not been encountered in children may be insufficient exposure to the drug because of considerably lower serum concentrations reached in children at the doses used.

Experience with the use of EMB in children is summarised in Table 5. The papers listed in the table document that 3811 children have received EMB, with only two (0.05%) developing possible ocular toxicity.

Pharmacokinetics of EMB in adults and children

> The true maximum dose is the highest dose that a patient can tolerate, hopefully while achieving the desired therapeutic response.
>
> —Charles A Peloquin, 1998[106]

In early pharmacology studies, serum concentrations of EMB were maximal 'at about 2 h' and peak concentrations were 10 μg/ml and 5 μg/ml following doses of 50 mg/kg body weight and 25 mg/kg, respectively. Serum concentrations were proportional to dose, and less than 10% of the dose administered was present in the serum after 24 h. There was no evidence of accumulation of the drug over more than 3 months. Within 6 h, 28% of an oral dose was excreted in the urine.[44] Following 17 mg/kg a 2-h value of 2 μg/ml was reached. A daily peak of 5 μg/ml was associated with high efficacy in mice[2] and monkeys.[107] It was noted that the response in monkeys was 'dose related over daily intakes of 12.5 to 100 mg/kg', and that when given in the company of INH 'serum levels of 0.6 to 2.0 μg/ml were associated with optimal benefits'.[107]

The percentage of EMB excreted unchanged has been variously reported as 40–80%[15] and 54–67%.[48] It has also been speculated that the considerable variation in absorption that has been reported and the somewhat delayed absorption found with EMB may be due to binding in the gastrointestinal tract.[48] One of the most recent published reports of the pharmaco-

Table 5 Occurrence of ocular toxicity associated with the use of EMB in children

Authors	*n*	Age, years	EMB dose, months (mg/kg/day)	Treatment duration, months	Toxicity
Chavarria et al. (1967)[94]	15	2–16	25	12–24	'. . . nor were there any manifestations of toxicity.'
Del Principe et al. (1968)[95]	58	1–12	3 (30) then 3 (15–20)	6	EMB was '. . . always well tolerated.'
Chavaria et al. (1970)[86]	36	0.3–16	1 (25) then 15	2–6	'We have never observed toxicity during 4 years of use of ethambutol '
Mankodi et al. (1970)[84]	16	3–12	3 (25) then 15	8–18	'In one child there was minimal edema of the optic disc after 7 months of therapy; however there were no visual symptoms.'
					Treatment was stopped for 4 months and reintroduced without complication.
Patwardhan et al. (1970)[96]	20	0.6–5	25	12	'. . . no toxic effects were noted.'
Schmid (1970)[97]	80	1–6	25	3–4	'No changes . . . in the eyes (visus or fundus) were observed.'
Simon (1970)[98]	49	?	15	3	'Dose: 15 mg/kg, because children cannot sufficiently describe secondary effects.'
Pilheu (1970)[10]	34	?	15	12	'Periodic . . . complete opthalmological examinations . . .' No visual abnormalities noted.
Mérida de Leon (1971)[99]	20	3–13	2 (25) then 15	8–12	None: '. . . no aparición de daño en el campo visual.'*
Scheffler (1971)[87]	60	3.5–15	3 (25) then 15–20	6 (average)	'Temporary disturbance of vision during the administration of ethambutol in two cases was not connected with the use of ethambutol and disappeared without interruption of the treatment.'
Benkert et al. (1974)[56]	26	3–14	15–25	—	'No side effect was caused in any case.'
Dingley & Sehgal (1974)[100]	54	2–14	2 (25) then 4 (15)	6	'. . . no ophthalmologic abnormalities were detected in the patients treated with ethambutol.'
Bhatia & Merchant (1975)[101]	54	0.2–5	3 (25) then 12 (15)	15	'No untoward effects were seen in our series of children given ethambutol for 6–18 months.'
Schmid (1981)[91]	2634	3–14	15–25	6	'. . . keine Komplikationen und keine toxishen Schädigungen beobacht. Trotzdem halten wir regelmäßige Visuskontrollen (Geschtsfeld, Farbshen, Augenhintergrund) fürangezeicht.'†
Gramer et al. (1982)[102]	6		20	9	'Visual acuity, visual field and mean retinal threshold of the central field revealed no significant changes with increasing cumulative ethambutol doses up to 166 g.'
Junnanond et al. (1983)[89]	27	5.5–15	20	2–24	'In this study there were no abnormal ocular changes in any of the patients.'
Fox quoted by Ramachandran et al. (1986)[92]	45	1–15	15–20	9–18	'There was no evidence from any of the assessments in any patient of ocular toxicity due to ethambutol.'
MRC TB & Chest Diseases Unit (1989)[71]	151	<1–14	6–12 (21%) 13–17 (50%) 18–30 (29%)	⩽2 (50%) ⩽6 (86%)	'In this survey . . . only one possible case of ocular toxicity was reported in 151 children receiving the drug, many in doses higher than those recommended and for a longer period.'
Mir et al. (1990)[103]	11	Mean 8	15–25	2	'Only one of the children had to discontinue therapy for a pyrazinamide intoleration.'
Seth et al. (1991)[90]	47	3–13	20	12	'. . . children do not seem to be at greater risk for developing ethambutol-induced optic damage as compared to adults . . . provided appropriate dosage schedules are adhered to.'
Singh et al. (1992)[104]	104	0.75–18	15	12–14	'The protocol of chemotherapy . . . produced satisfactory results without any side effect . . .'
Palme et al. (2002)[105]	250	0–14	15–25	2–12	'. . . we found no case of impaired vision associated with ethambutol therapy . . .'
Zhu et al. (2004)[53]	14	0.2–17	13–26		Transient blurred vision in one child. Treatment continued.

* No apparent visual field defects detected.
† No complications or toxic effects observed despite ophthalmological follow-up (visual fields, colour vision and fundoscopy).
EMB = ethambutol; MRC = Medical Research Council.

kinetics of EMB in children found slow and incomplete absorption of EMB.[53]

More sophisticated studies have confirmed the above observations.[48,52,53,57,108] These have confirmed that most of the drug (approximately 80%) is excreted unchanged in urine, that the time to maximal serum concentration (T_{max}) tends to be delayed in comparison to other drugs (between 2–4 h), and that following a meal

a lower maximal serum concentration (C_{max}) is found than when fasting (4.5 μg/ml vs. 3.8 μg/ml after a dose of 25 mg/kg).

With the notable exception of the central nervous system, the tissue distribution of EMB has been good, and tissue concentrations higher than in serum or plasma have been found in patients[105] and experimental animals.[110,111] In an exception to these findings, the concentration of EMB in abscess pus was considerably less than in accompanying serum in two studies.[50,112]

EMB serum concentrations in children receiving EMB doses varying from 15 to 35 mg/kg have been determined by several groups,[53–56] but HIV-infected children were assessed in only one study.[57] All of these studies found EMB serum concentrations in children to be lower than in adults following similar dosages. Furthermore, Hussels et al. also found lower serum concentrations in younger children than in older children.[54,55] Commenting on this, Schmid[91] stated that it was his practice to use EMB in children at a dosage of 20 mg/kg, to increase this by 5 mg/kg in those aged <3 years and to reduce it by 5 mg/kg in those aged >11 years. By this means, taking into account the serum concentrations of EMB, they would avoid toxicity but achieve effective therapeutic concentrations (defined as >2 μg/ml) in the majority of children. He stated that they had treated 2634 children without experiencing any toxic damage. Regular evaluation of the eyes was undertaken.

Published maximum serum concentrations of EMB in adults and children determined by various methodologies appear in Tables 2 and 3, respectively and the maximum serum concentrations of EMB in children and adults are illustrated in Figure 2. The serum concentrations reached in adults and children after receiving similar doses of EMB are clearly different. This figure suggests that to achieve EMB serum concentrations in a child equivalent to those in an adult following a dose of 15 mg/kg might require a dose of 25 mg/kg or higher. It should be noted that none of the published pharmacokinetic studies included children less than 1 year of age. As infancy is a period of particularly rapid flux in the body's handling of drugs and toxins, studies of the kinetics of EMB in infants are urgently needed.

Several factors influencing pharmacokinetics are subject to age-related variations, including the ratio of extracellular to intracellular and total body water, biotransformation and elimination.[113,114] These and other aspects should be kept in mind in considering the above results. As EMB excretion is predominantly renal, it should be noted that values for glomerular excretion increase rapidly following birth and reach adult values between 2.5 and 5 months.

Published recommendations for the use of EMB in children

Published recommendations for the use of EMB in children are summarised in Table 6. The recommended dosages reflect those in other contemporary literature. Thus, earlier recommendations advise 25 mg/kg for the first 2 months or 8 weeks, followed by 15 mg/kg; later recommendations suggest 15 mg/kg throughout. Although more recent recommendations reflect a more liberal approach to the use of EMB in children, this tends to be balanced by the use of 'hedging' statements such as '. . . particular caution may be warranted'.[121]

CONCLUSIONS

In debating what dose of EMB children should receive, several factors need to be considered:

1 Is it necessary for children to be exposed to the same serum concentrations of EMB as adults?
2 If children are exposed to the same serum concentrations of EMB as adults (and this might mean a dose of 25–30 mg/kg EMB or higher), will children then not be exposed to the same risks of ocular toxicity as adults?
3 Children receiving an EMB dose of 15 mg/kg will probably reach a peak serum concentration of slightly more than 1 μg/ml. As the sliding scale necessitated by the use of body weight bands gets closer to 20 mg/kg, it seems likely that the mean maximum serum concentration will also get closer to 2 μg/ml. In the light of certain in vivo and in vitro experimental data, is this perhaps just sufficient to achieve the somewhat limited therapeutic aims that we have for EMB in current regimens, i.e., the protection of companion drugs against resistance and the prevention of further resistance in the presence of existing resistance?

The published evidence indicates that peak serum concentrations of EMB achieved in children are significantly lower than those in adults receiving a similar mg/kg body weight dose. Published data also indicate that both the efficacy and the toxicity of EMB in adults are dose-related. At a daily dose of 15–20 mg/kg body weight in adults, EMB can be considered no more than bacteriostatic and will provide a measure of protection against the development of resistance in companion drugs and against the further expansion of existing resistance. With regard to ocular toxicity, this can still occur in adults at a daily dose of 15–20 mg/kg, but is relatively rare and will usually occur only after several months of treatment.

On considering this evidence, one is left with the uneasy feeling that ocular toxicity has so seldom been documented in children because children are exposed to serum concentrations of EMB insufficient to be as clinically effective as in adults. The reverse implication is that the currently recommended doses of EMB are unlikely to carry a serious risk of ocular toxicity to children and can be recommended for use in children of all ages. Schmid's proposal[91] draws upon clinical experience and the use of body surface area for

Table 6 Published recommendations for the dosage of EMB in children

Source	Dose (mg/kg)		Comments
	Daily	Intermittent	
Horne (1990)[115]	25/15*	30 (3×/week) 45 (2×/week)	'Ethambutol is best avoided in children too young for objective eye tests . . .'
Chaulet et al. (1992)[116]	25/15*	—	'. . . most paediatricians are reluctant to prescribe ethambutol in children under 12.'
American Thoracic Society (1994)[117]	15–20	—	'Ethambutol is generally not recommended for children whose visual acuity cannot be monitored (<8 years of age). However, ethambutol should be considered for all children with organisms resistant to other drugs when susceptibility to ethambutol has been demonstrated or susceptibility is likely.'
Starke & Correa (1995)[118]	15–25	50 (2×/week)	'Although ethambutol has not been used extensively in young children, ophthalmological toxicity in children has not been reported with an ethambutol dosage of 15 mg/kg/day and the drug may be used carefully.
British Thoracic Society (1998)[119]	15	30 (3×/week) 50 (2×/week)	'Because of the possible (but rare) toxic effects of ethambutol on the eye, it is recommended that visual acuity should be tested by Snellen chart before it is first prescribed. The drug should only be used in patients who have reasonable visual acuity and who are able to appreciate and report visual symptoms or changes in vision. . . . In small children and in those with language difficulties ethambutol should be used where appropriate . . .'
American Academy of Pediatrics (2000)[120]	15–25	50 (2×/week)	' . . . use of ethambutol in young children whose visual acuity cannot be monitored requires careful consideration of risks and benefits.'
Rieder (2002)[121]	15 (15–20)	—	'It has been recommended not to use ethambutol in children too young for objective tests for visual acuity. There is, however, no evidence that children are particularly prone to ocular toxicity, and ethambutol may thus be used in children. However, as children might be less likely to report ocular toxicity, particular caution may be warranted.'
WHO Stop TB Department (2003)[4]	15 (15–20)	—	'There has been understandable caution with the use of ethambutol in children too young to report early visual deterioration, but ethambutol has been safely used in infants and young children at recommended dosages.'
WHO Model Formulary (2005)[7]	15	—	'Contraindications: optic neuritis; children under 5 years—unable to report symptomatic visual disturbances'
Department of Child and Adolescent Health and Development, WHO (2005)[8]	20 (15–25)	30 (25–35) (3×/week)	

* 25 mg/kg for 2 months followed by 15 mg/kg for the remainder of treatment.
EMB = ethambutol; WHO = World Health Organization; TB = tuberculosis.

dosage calculation, and represents a compromise between efficacy and the smallest risk of toxicity, i.e., 20 mg/kg, but reduced to 15 mg/kg in children aged >11 years and increased to 25 mg/kg in children aged <5 years. This would, however, be a somewhat complicated regimen to propose for use under NTP conditions and would require considerably more data to substantiate its value.

Taking into account the number of children aged from <1 to 18 years who have been treated with EMB with doses varying from 15 to 30 mg/kg/day without overt ocular toxicity, this review supports a

recommended daily dose of 20 mg/kg (range 15–25) body weight for children of all ages. Increasing the EMB dose above this range to compensate for the deficiencies in serum concentrations that have been identified in children might well bring an increased risk of EMB ocular toxicity. The evidence presented in this review has informed WHO's new policy to recommend a daily dose of 20 mg/kg (range 15–25) in the treatment of children of all ages with drug-susceptible TB.[122] For intermittent treatment, doses of 30 mg/kg (range 20–35) three times weekly or 45 mg/kg (range 40–50) twice weekly are proposed, as is currently recommended for adults. As with adults, care should be taken to establish that the child does not suffer from renal disease as this could cause exposure to unacceptably high serum concentrations of EMB.

Should the use of EMB be necessitated by drug-resistant TB in a young child, it would also seem prudent, weighing up the relative dangers of toxicity vs. efficacy and the dangers of drug-resistant TB, that the use of a higher range of daily doses (20–30 mg/kg) should be considered in a child of any age.

It goes almost without saying that more studies and data are needed with regard to the pharmacokinetics of EMB in the paediatric age group, especially in infants and younger children, on which to base objective therapeutic decisions.

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RÉSUMÉ

La dose quotidienne d'éthambutol (EMB) actuellement recommandée pour le traitement de la tuberculose chez les enfants varie d'une dose quotidienne maximum de 15 mg/kg de poids corporel (sans valeurs extrêmes) jusqu'à des doses de 15–20 mg/kg et de 20 mg/kg (extrêmes 15–25 mg/kg). Nous avons revu les données objectives publiées concernant le dosage, la toxicité et la pharmacocinétique de l'EMB chez les enfants et les adultes et recommandé une dose d'EMB pour l'utilisation pédiatrique. Nous avons mené des recherches sur Medline en utilisant les mots-clé éthambutol, enfance, tuberculose, pharmacocinétique, biodisponibilité et toxicité ; on a recherché les références croisées à partir des papiers originaux, des livres et des comptes-rendus de conférences depuis 1961. Lorsque les résumés anglais étaient disponibles, nous avons également prélevé les données dans des articles en langages autres que l'anglais.

L'efficacité de l'EMB est liée à la dose, principalement lorsqu'il est donné aux adultes, que ce soit isolément ou avec un seul autre médicament. En combinaison avec l'isoniazide (INH), une dose de 15 mg/kg d'EMB donne des résultats meilleurs que 6 mg/kg ; 25 mg/kg donne des résultats meilleurs que 15 mg/kg. L'apparition d'une toxicité oculaire est également liée à la dose ; aux doses supérieures à 50 mg/kg, plus de 40% des adultes souffrent de toxicité, alors qu'elle n'est que de 0–3% à la dose de 15 mg/kg/jour. Les pics de concentration sérique de l'EMB augmentent en rapport avec la dose, mais chez les enfants sont significativement plus faibles à dose égale. L'EMB n'a été arrêté en raison d'une toxicité oculaire possible que chez deux de 3811 enfants (0,05%) recevant des doses d'EMB de 15 à 30 mg/kg ; les enfants de tous âges peuvent recevoir l'EMB à des doses quotidiennes de 20 mg/kg (extrêmes 15–25 mg/kg) ainsi que des doses intermittentes de 30 mg/kg/poids corporel par semaine, sans crainte injustifiée.

RESUMEN

La dosis diaria de etambutol (EMB) recomendada actualmente en el tratamiento de la tuberculosis en los niños varía entre una dosis máxima diaria de 15 mg/kg de peso corporal (sin intervalo), de 15 a 20 mg/kg y 20 mg/kg (intervalo entre 15 y 25 mg/kg). En el presente artículo se analizan los datos publicados con respecto a la pauta posológica, la toxicidad y la farmacocinética del EMB en niños y adultos y se recomienda una dosis de EMB para uso pediátrico. Se realizaron búsquedas en la base de datos Medline con las palabras clave EMB, infancia, tuberculosis, farmacocinética, biodisponibilidad y toxicidad ; se buscaron referencias cruzadas en las publicaciones originales, libros e informes de conferencias a partir de 1961. Cuando se contó con resúmenes en inglés, se extrajeron los datos de artículos publicados en otros idiomas.

El EMB presenta una eficacia relacionada con la dosis, que puede evaluarse mejor cuando se administra a adultos en forma aislada o con un solo medicamento adicional. Asociado con isoniacida (INH), el EMB en dosis de 15 mg/kg dio mejores resultados que en 6 mg/kg y 25 mg/kg fueron superiores a 15 mg/kg. La aparición de toxicidad ocular se relacionó también con la dosis ; con dosis superiores a 50 mg/kg, más del 40% de los adultos presentaron toxicidad y de 0% al 3% con dosis de 15 mg/kg diarios. La concentración sérica máxima de EMB aumentó con la dosis, pero fue significativamente inferior en niños que recibían la misma pauta posológica. Sólo en 2 de 3811 niños (0,05%) que recibieron dosis de EMB de 15 a 30 mg/kg se suspendió el EMB por posible toxicidad ocular ; los niños de todas las edades pueden recibir en forma segura EMB en dosis diarias de 20 mg/kg (intervalo de 15 a 25 mg/kg) y dosis intermitentes tres veces por semana de 30 mg/kg de peso corporal.