

Ethambutol efficacy and toxicity: literature review and recommendations for daily and intermittent dosage in children



**World Health
Organization**

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Contents

Abbreviations	iii
Foreword	iv
Contributors	v
Acknowledgements.....	v
Summary	vi
1. Introduction	1
2. Methods	3
3. Results.....	4
3.1 Efficacy of ethambutol in adults	4
3.2 Toxicity of ethambutol in adults.....	6
3.3 Efficacy and toxicity of ethambutol in children	7
3.4 Pharmacokinetics of ethambutol in adults and children	8
3.5 Published recommendations for the use of ethambutol in children	9
4. Conclusions	10
References	11
Annex I.....	26
Efficacy of ethambutol in adults	26
Annex II.....	34
Toxicity of ethambutol in adults.....	34
Annex III.....	51
Efficacy and toxicity of ethambutol in childhood	51
Annex IV	58
Pharmacokinetics of ethambutol in adults and children.....	58
Annex V	66
Published recommendations for the use of ethambutol in children	66

Abbreviations

AFB	acid-fast bacilli
$C_{\max}$	maximum plasma concentration
CPM	capreomycin
CS	cycloserine
EBA	early bactericidal activity
EMB	ethambutol
ETH	ethionamide
FDC	fixed-dose combination
INH	isoniazid
KM	kanamycin
MIC	minimum inhibitory concentration
PSA	<i>p</i> -aminosalicylic acid
PZA	pyrazinamide
RMP	rifampicin
SM	streptomycin
$T_{\max}$	time to reach $C_{\max}$
TB	tuberculosis
THIO	thioacetazone
VEP	visual evoked potential
VIO	viomycin

In addition to the above abbreviations, used for convenience in the text of this review, there is a standard code for TB treatment regimens, which uses an abbreviation for each anti-TB drug. A regimen consists of two phases. The number in front of each phase represents the duration of that phase in months. A subscript number (e.g. ₃) following a letter (drug abbreviation) is the number of doses per week of that drug. If there is no subscript number following a letter, treatment with that drug is daily. An alternative drug (or drugs) appears as a letter (or letters) in parentheses.

Example: 2 SHRZ/4 H₃R₃

The *initial phase* is 2 SHRZ. Duration of the initial phase is 2 months. Drug treatment is daily (no subscript numbers after the letters) with streptomycin (S), isoniazid (H), rifampicin (R) and pyrazinamide (Z).

The *continuation phase* is 4 H₃R₃. Duration of the continuation phase is 4 months, with isoniazid and rifampicin three times weekly (subscript number after the letters).

Foreword

A literature review commissioned by the Stop TB Department of World Health Organization was prompted by the varying recommendations in the literature, including WHO publications, with regard to the dose of ethambutol for the treatment of tuberculosis (TB) in children. Examples of WHO recommendations include the following:

- *WHO model list of essential medicines: 14th list, March 2005*, which recommends a daily dose of 15 mg/kg (without a range) and includes the advice that ethambutol should not be given to children under 5 years of age.
- *Pocket book of hospital care for children: guidelines for the management of common illnesses with limited resources*, 2005, issued by the Department of Child and Adolescent Health and Development, which recommends a daily dose of 20 mg/kg (range 15–25 mg/kg).
- *Treatment of tuberculosis: guidelines for national programmes*, 2003, issued by the Stop TB Department, which recommends a maximum dose of 15 mg/kg (without a range).

This document reviews the published evidence relating to the dosage, toxicity and pharmacokinetics of EMB in children and adults and makes a recommendation for the dosage of EMB to be used in childhood that represents the best compromise between efficacy and toxicity.

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Summary

Introduction

Current recommendations by WHO and other bodies for the dosage of ethambutol (EMB) in children vary from a maximum daily dose of 15 mg/kg body weight daily (without a range) to daily doses of 15–20 mg/kg and of 20 mg/kg with a range of 15–25 mg/kg. This document reviews the published evidence relating to the dosage, toxicity and pharmacokinetics of EMB in children and adults and makes a recommendation for the daily dose of EMB to be used in children. The conclusion also contains a recommendation for an intermittent dose.

Method

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

Results

EMB has a clear dose-related efficacy that is best seen when it was given to adults alone, or in the company of only a single other drug; thus given together with isoniazid (INH) a dose of 15 mg/kg EMB gave better results than a dose of 6 mg/kg, and a dose of 25 mg/kg better results than 15 mg/kg. The occurrence of ocular toxicity in adults was also dose related and at doses of >50 mg/kg >40% of adults developed toxicity compared with 0–3% at a dose of 15 mg/kg/daily. Peak serum EMB concentrations in both children and adults increase in relation to dose, but are significantly lower in children than adults receiving the same mg/kg/body weight dose. In only 2 of 3811 children (0.05%) recorded as having received doses varying from 15 mg/kg to 30 mg/kg was EMB stopped for possible EMB ocular toxicity.

Conclusion

In view of the almost total lack of ocular toxicity in children of all ages receiving EMB at doses of from 15–30 mg/kg documented in this review it can be recommended that 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.

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