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Efficacy and tolerability of ethionamide versus prothionamide: a systematic review



To the Editor:

To treat multidrug-resistant tuberculosis (MDR-TB), the World Health Organization recommends to include, during the intensive phase of treatment, at least a parenteral agent, a later-generation fluoroquinolone, ethionamide (Eth) (or prothionamide (Pth)), cycloserine (Cs) or *p*-aminosalicylic acid (PAS) if Cs cannot be used, and pyrazinamide (Pzd) (which is not considered among the aforementioned four probably effective drugs) [1, 2]. In particular, among the four drugs likely to be effective, at least two essential or “core” drugs (one with a good bactericidal and one with a good sterilising activity) and two other “companion” drugs should be administered [3, 4].

In most of the countries where drug susceptibility testing cannot be performed to guide treatment regimen design, standardised second-line treatment regimens are prescribed, based on kanamycin (Km), levofloxacin (Lfx), Eth, Cs and Pzd. Although the regimen is built following the international recommendations, the outcomes remain poor globally [5, 6]. Less than 50–70% of the cases, in fact, achieve treatment success [5, 6], resulting in insufficient control of MDR-TB. It is widely recognised that one frequent cause of poor outcome is treatment default, which is mostly due to the low tolerability of the antituberculosis drugs employed [7]. One of the less tolerated antibiotics is Eth, because of the serious and frequent gastric adverse events [8–9] or of hypothyroidism, which is frequently subclinical.

Eth and Pth are thionamide drugs, characterised by a structure similar to isoniazid (Inh). They inhibit the mycobacterial synthesis of mycolic acid through a specific action against the *inhA* product enoyl-acyl carrier protein reductase; thus, they can be classified as bactericidal. However, their metabolic process is poorly known and, therefore, it is difficult to understand the pathogenesis behind the occurrence of adverse events following their administration.

If the reasons behind the choice of Km, Lfx, Cs and Pzd are in general easy to explain (although they do not necessarily represent the best choice), less clear is the reason why Eth is used in the majority of the programmes instead of Pth. For this reason, we have carried out a systematic review on the existing evidence focused on efficacy and tolerability of Eth *versus* Pth.

The search was performed using the search engine PubMed, without any time restriction. Only articles written in English, French, Spanish and Italian were selected. The following keywords were used to retrieve the scientific references related to the research question: “ethionamide”, “prothionamide”, “efficacy”, “safety” and “tolerability”.

Reviews, case reports, case series and letters were excluded. References of the selected articles were analysed in order to identify significant manuscripts not found by the search engine.

We adopted a simplified five-point checklist adapted from that of the Scottish Intercollegiate Guidelines Network to grade the quality of the scientific evidence. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flowchart was used to summarise the search and selection process (figure 1).

We found only six articles addressing this issue, all of them published before 1970. The core information derived from these articles is summarised in table 1. In the “double blind” trial by CHAMBATTE *et al.* [10], published in 1965, Pth was compared to Eth (1 g·day⁻¹). Tolerability was reported to be very good by 62%

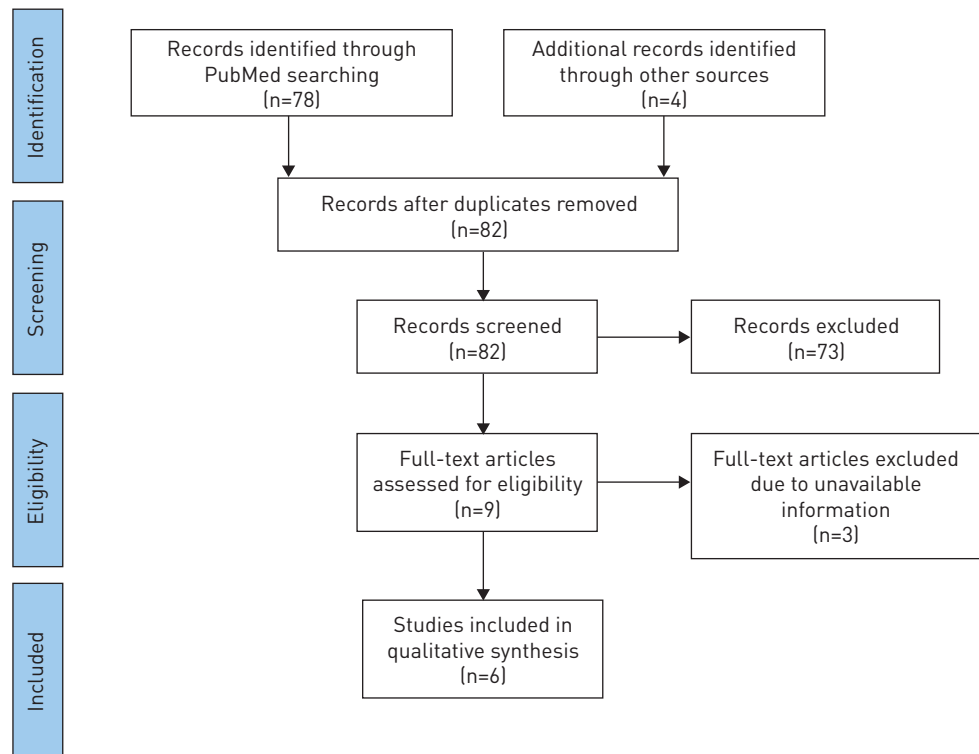


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram.

patients receiving Pth, while only 24% of those receiving Eth reported that it was tolerable. Eth and Pth were both prescribed in combination with another two or three antituberculosis drugs, and the regimens were not standardised.

In a Japanese study published in 1968 [11], 531 tuberculosis cases were divided into three groups: in Group 1, patients received streptomycin (Sm), Inh and PAS; in Group 2, Sm, Inh and Eth; and in Group 3, Sm, Inh and Pth. The thionamides were prescribed at a daily dosage of 500 mg. The sputum conversion rates were similar in the three groups (96%, 98% and 96%, respectively), while the rate of adverse events was statistically higher in the Eth arm (75% versus 60%, respectively). However, no significant difference was reported in terms of treatment interruption. Notably, Group 1 patients, who were not treated with thionamides, showed a toxicity rate of only 32%.

In the double-blind British Tuberculosis Association study, published in 1968 [12], 53 patients receiving Pth (750 mg), in addition to Sm and Inh, were compared with 48 patients receiving Eth (750 mg) and the same backbone drugs for 10 weeks. Gastric intolerance was more frequent in the Eth group (50%) than in the Pth group (32%), although the difference was not statistically significant. Additionally, minor adverse events were more frequent with Pth, while severe side-effects were more frequent with Eth, even if the differences were not statistically significant. The liver impairment rate was similar in the two groups. Furthermore, higher weight gain, probably attributed to a better gastrointestinal tolerability of Pth, was found in those who received Pth compared to those receiving Eth.

The double-blinded study by Fox *et al.* [13], published in 1969, compared the tolerability of Eth and Pth in 128 African patients, using different dosages in intermittent regimens; in addition, the effect of the vitamin B complex in reducing potential adverse events was also evaluated. The incidence and severity of adverse events for Eth (at doses ranging from 0.25 to 1.75 g daily) and Pth (at doses ranging from 1.25 to 1.75 g daily) were compared with a placebo-administered group. Females reported more adverse events following exposure to both drugs than males, but the differences between Eth and Pth were not significant. However, males showed significantly ($p < 0.005$) more adverse events with Eth (36%) than Pth (17%), with significant differences for gastric intolerance ($p < 0.01$), vomiting ($p < 0.01$) and headache ($p < 0.003$). Furthermore, one or more adverse events occurred more frequently when the dosage of Eth increased, but a trend between dosage and side-effects was not observed in the case of Pth. The addition of the vitamin B complex had no effect on the incidence of new adverse events.

TABLE 1 Findings and characteristics of the available studies comparing tolerability and efficacy of ethionamide (Eth) versus prothionamide (Pth)

Study [ref.]	Year	Design	Number of patients enrolled	Treatment regimen	Dosage of Eth/Pth and other drugs in the regimen	Adverse events due to Eth/Pth	Treatment interruption due to Eth/Pth adverse events	Sputum smear and culture conversion
CHAMBATTE <i>et al.</i> [10]	1965	Double blind		Pth group: +2 or 3 anti-TB drugs Eth group: +2 or 3 anti-TB drugs	Eth: 1 g·day ⁻¹ Pth: 1 g·day ⁻¹	Pth tolerability: 62% Eth tolerability: 24%		
Japanese study [11]	1968	Controlled	For the clinical analysis Group SHP: 105 Group SHI4T: 109 Group SH2I T: 100 For analysis of drug tolerance and toxicity: Group SHP: 167 Group SHI4T: 167 Group SH21T:160	Group SHP: Sm, Inh, PAS Group SHI4T: Sm, Inh, Eth Group SH2I T: Sm, Inh, Pth	Group SHP: Sm: 1 g twice weekly Inh: 300 mg twice daily PAS: 10 g three doses daily Group SHI4T Sm: 1 g twice weekly Inh: 300 mg twice daily Eth: 500 mg twice daily Group SH2I T Sm: 1 g twice weekly Inh: 300 mg twice daily Pth: 500 mg twice daily	Gastro-intestinal disturbance Group SHI4T: 56 (33.5%) Group SH2I T: 41 (25.6%) Liver damage Group SHI4T: 13 (7.8%) Group SH2I T: 19 (11.9%) Tinnitus Group SHI4T: 5 (3.0%) Group SH2I T: 4 (2.5%) Diminution of hearing Group SHI4T:2 (1.2%) Group SH2I T: 1 (0.6%) Rash Group SHI4T:6 (3.6%) Group SH2I T: 3 (1.9%) Joint pains Group SHI4T:8 (4.8%) Group SH2I T:6 (3.8%) Hypoesthesia Group SHI4T: 11 (6.6%) Group SH2I T: 7 (4.4%) Headache Group SHI4T: 12 (7.2%) GroupSH2I T: 5 (3.1%) Insomnia Group SHI4T:7 (4.2%) GroupSH2I T:7 (4.2%) Fever Group SHI4T: 0(0%) GroupSH2I T: 1 (0.6%) Vertigo Group SHI4T: 1 (0.6%) GroupSH2I T: 0 (0%) Neuropsychiatric reaction Group SHI4T: 3 (1.8%) Group SH2I T:1 (0.6%)	Withdrawals after 3 months due to toxicity Group SHP: 3 (2.9%) Group SHI4T: 10 (9.2%) Group SH2I T: 9 (9.0%)	Group SHP: 96% Group SHI4T: 98% Group SH21T: 96%
British study [12]	1968	Double blind	Group Eth: 48 Group Pth: 53	Group Eth: Eth, Inh, Sm Group Pth: Pth, Inh, Sm	Pth: 375 mg twice daily Eth: 375 mg twice daily Inh: 150 mg twice daily Sm: 0.75 mg or 1g [#] once daily	Gastric intolerance Group Eth: 24 (50%); severe symptoms in 9 (19%) Group Pth: 17 (32%); severe symptoms in 3 (6%) Abnormal liver function tests Group Eth: 5(10%) Group Pth: 5(9%) Headache Group Eth: 11 (23%) severe symptoms in 2 (4%) Group Pth: 5 (9%) severe symptoms in 1(2%) Sleepiness Group Eth: 3 (6%) severe symptoms in 1(2%) Group Pth: 8 (15%) Insomnia Group Eth: 4 (8%) Group Pth: 2 (4%)	Group Eth 6 (13%) withdrawn due to abnormal liver function tests: 5 (10%) sleepiness: 1 (2%) 1 (2%) treatment interrupted for 1 week due to gastrointestinal intolerance Group Pth: 9 (17%) withdrawn due to abnormal liver function tests: 5 (9%) gastrointestinal intolerance: 2 (4%)	NA

Continued

TABLE 1 Continued

Study [ref.]	Year	Design	Number of patients enrolled	Treatment regimen	Dosage of Eth/Pth and other drugs in the regimen	Adverse events due to Eth/Pth	Treatment interruption due to Eth/Pth adverse events	Sputum smear and culture conversion
Fox et al. [13]	1969	Double blind	Group A-B: 6 (49 days) Group C-D: 6 (49 days) Group E-H: 6 (49 days) Group I-L: 20 (21 days)	Group A-B: Sm, Inh, Eth, ST Group C-D: Sm, Inh, Eth, ST Group E-H: Sm, Inh, Eth, Pth, ST Group I-L: Sm, Inh, Eth, Pth, vitamin B complex additive	Group A-B Sm: 0.75 g once daily Inh: 300 mg once daily Eth: 1.25-0.00 g once daily (5 days) ST: 43 days (+placebo test dose) Group C-D Sm: 0.75 g once daily Inh: 300 mg once daily Eth: 1.75-0.50 g once daily (5 days) ST: 44 days (no placebo test dose) Group E-H Sm: 0.75 g once daily Inh: 300 mg once daily Eth 1.75-1.25 g once daily (5 days) Pth: 1.75-1.25 g once daily (5 days) ST: 44 days (no placebo test dose) Group I-L Sm: 0.75 g once daily Inh: 300 mg once daily Eth: 1.75-0.0 g once daily Pth: 1.75-1.25 g once daily Vitamin B complex additive: once daily (10 patients only, random)	Depression Group Eth: 5 (10%) Group Pth: 3 (6%) Paraesthesia Group Eth: 3 (6%) Group Pth: 2 (4%) severe symptoms in 1(2%) Acne Group Eth: 3 (6%) Group Pth: 5 (9%) Skin pigmentation Group Eth: 2 (4%) Group Pth: 0 (0%) Alopecia Group Eth: 1(2%) Group Pth: 3 (6%) Overall, for all 12 groups, a total of 140 adverse events was recorded for 87 (29.3%) of the 297 doses of Eth, 76 for 45 (27.4%) of the 164 doses of Pth and 174 for 150 (4.8%) of the 3099 days on which doses of placebo were given Vomiting Eth: 30(10%) Pth: 17 (10%) Nausea Eth: 16 (5%) Pth: 7 (4%) Other Gastric Eth: 18(6%) Pth: 14 (9%) Giddiness Eth: 31 (10%) Pth: 21 (13%) Headache Eth: 26 (9%) Pth: 6 (4%) Fever Eth: 5 (2%) Pth: 4 (2%) Visual disturbances Eth: 2 (1%) Pth: 4 (2%) Cutaneous Eth: 1 (0%) Pth: 0 (0%) Aches and pains Eth: 3 (1%) Pth: 1 (1%) Miscellaneous Eth: 8 (3%) Pth: 2 (1%)	acute psychosis: 1 paraesthesia: 1(2%) 1 (2%) treatment interrupted for 1 week due to severe headache	No data

Continued

TABLE 1 Continued

Study [ref.]	Year	Design	Number of patients enrolled	Treatment regimen	Dosage of Eth/Pth and other drugs in the regimen	Adverse events due to Eth/Pth	Treatment interruption due to Eth/Pth adverse events	Sputum smear and culture conversion
ANASTASATU <i>et al.</i> [14]	1969		Group Eth: 26 Group Pth: 26	Group Eth: Eth, cycloserine, viomycin Group Pth: Pth, cycloserine, viomycin	NA	Gastric intolerance Group Eth: 46% Group Pth: 23%	Group Eth: 3 Group Pth: 1	Group Eth: 45% Group Pth: 70%
VERBIST[15]	1969	Double blind	Group Pth: 30 Group Eth-B: 24 Group Eth-HCl: 25 Group THC: 26	Group Pth: Sm, Inh, Pth Group Eth-B: Sm, Inh, Eth-B Group Eth-HCl: Sm, Inh, Eth-HCl Group THC: Sm, Inh, THC	Group Pth Sm: 1 g once daily Inh: NA Pth: 1 g once daily Group Eth-B Sm: 1 g once daily Inh: NA Eth: 1 g once daily Group Eth-HCl Sm: 1 g once daily Inh: NA ETH-HCL: 1 g once daily Group THC Sm: 1 g once daily Inh: NA THC: 6 g	Increase serum transaminase values Group Pth 17 (57%) Group Eth-B: 10 (20%) Gastric upset Group Pth: 17 (57%) Group Eth-B: 36(73%) Stomach ache Group Pth: 4 (13.3%) Group Eth-B: 5 (21%) Gastric burning Group Pth: 6 (20%) Group Eth-B: 9 (37.5%) Bad taste Group Pth: 4 (13.3%) Group Eth-B: 12 (50%) Nausea vomiting Group Pth: 10 (33.3%) Group Eth-B: 8 (33.3%) Anorexia Group Pth: 12 (40%) Group Eth-B: 12 (50%) Headache Group Pth: 2 (6.6%) Group Eth-B: 3 (12.5%) Shoulder or muscle pain Group Pth: 3 (10%) Group Eth-B: 3 (12.5%) Psychasthenic complaints Group Pth: 8 (26.6%) Group Eth-B: 3 (12.5%)	Group Pth 7 (23.3%) changed therapy due to high levels of serum transaminase 4 (13.3%) due to nausea-vomiting and anorexia 1 (3.3%) due to severe headache and gynecomastia Group Eth-B 9 (37.5%) changed therapy due to gastric troubles, nausea and/or anorexia 1 (4.1%) due to pain in the joints	No data

TB: tuberculosis; SHP: streptomycin, isoniazid and sodium *p*-aminosalicylate; SHI4T: streptomycin, isoniazid and Eth; SH2I T: streptomycin, isoniazid and Pth; Sm: streptomycin; Inh: isoniazid; PAS: *p*-aminosalicylic acid; NA: not available; ST: supplement tablets (placebo); Eth-B: ethionamide base; Eth-HCl: ethionamide hydrochloride; THC: thiocarlide (control).
#: dose of Sm was left to the discretion of the clinician.

In the study by ANASTASATU *et al.* [14], published in 1969, Eth and Pth were administered in two groups of 26 patients respectively, on top of Cs and viomycin. Gastric intolerance was reported in 46% of those receiving Eth (three patients interrupted the treatment) and in 23% only of those receiving Pth (one case interrupted the treatment). Culture conversion occurred in 45% of those treated with Eth and 70% of those treated with Pth, respectively. However, the small number of cases did not allow assessment of a statistically significant difference. The authors concluded that the results with Pth could be attributed to its better tolerability.

In another double-blinded study published in 1970 by VERBIST *et al.* [15], 1 g Pth administered in two daily doses was better tolerated than Eth (1 g, two daily doses), although it was associated with more frequent liver toxicity. 130 pulmonary tuberculosis patients were recruited and were prescribed a backbone regimen including Inh and Sm, together with either Pth, Eth, Eth hydrochloride or thiocarlide. The tolerability profile after 7 weeks was poorer in the two groups receiving Eth ($p < 0.025$), although those exposed to Pth showed more biochemical disorders ($p < 0.001$), especially increased serum transaminase values. Treatment discontinuation was reported in 12 out of 30 patients receiving Pth, in 10 out of 24 patients receiving Eth and 11 out of 25 patients receiving Eth hydrochloride.

Several limitations of this systematic review can be raised. The adoption of the single engine PubMed could have slightly reduced the search sensitivity, although the old and low number of the articles counterbalance this methodological choice. Furthermore, standardised definitions of efficacy, safety and tolerability were not adopted, the selected studies being very old and not following an internationally agreed-upon methodology. The quality of the scientific evidence focused on the clinical comparison between the two drugs was poor according to the grading system we adopted.

In conclusion, although the evidence is limited and rather old, Pth appears to be better tolerated (especially in terms of reduced frequency of gastric adverse events, although Pth-related liver toxicity was reported). According to the publications described here, the efficacy of the two thionamides is similar between studies, although some of them report a higher efficacy of Pth.

The findings of this systematic review seem to suggest, in absence of new evidence, to slightly prefer Pth to Eth in designing MDR-TB regimens. However, the quality of the retrieved scientific evidence is extremely poor, due to the design, implementation, and reporting of the studies dealing with the comparison of the two drugs; consequently, any firm conclusions in terms of preferences should be currently avoided.



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Prothionamide is slightly better than ethionamide in treating MDR-TB patients

<http://ow.ly/bSwY300i061>

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