# Pattern of ethionamide susceptibility and its association with isoniazid resistance among previously treated tuberculosis patients from India

Dear Editor,

Ethionamide (Eto), a structural analogue of isoniazid (INH), shares same cellular target in fatty acid synthesis, namely *inh*A.[1] It was hypothesized that low level of INH resistance can induce cross resistance to Eto.[2,3] But reports explaining the mechanism of cross resistance between Eto and INH are limited and are still being explored.[2,4] The present study was aimed at understanding the pattern of Eto susceptibility and its association with INH resistance from previously treated patients.

One hundred and seventy-six consecutive *Mycobacterium tuberculosis* strains isolated from patients failing Category I and II included in the study were subjected to drug susceptibility testing (DST) for isoniazid and ethionamide by minimum inhibitory concentration (MIC) method on Lowenstein-Jensen (LJ) medium following the standard protocol.[5] Pearson chi-square test at 5% level of significance using SPSS software version 14.0 was performed to assess the significance of association between susceptibility pattern of INH and Eto.

Of the 176 isolates, 78% and 22% were resistant and susceptible to INH. Eighty-one (49.6%) and 95 (59.3%) isolates showed resistant and susceptible phenotype towards Eto. Sixty-eight (39%) of the 176 isolates were resistant to INH and Eto where as 15% (26/176) were sensitive to both drugs. Resistance only to INH or Eto was observed in 39% and 7.3% of the isolates respectively (Table 1). There is an equal distribution (39%) of Eto susceptible and resistant strains among 137 INH resistant isolates. In contrast, among the INH susceptible strains, Eto susceptible isolates were twice in number than resistant isolates. Statistical analysis indicated insignificant association (p-value = 0.1) between the susceptibility profile of INH and Eto among study isolates.

The presence of high Eto resistance (46%) and co-resistance with INH (49.6%) among patients under treatment is in accordance with the previous reports.[6-8] It is a known fact that accurate Eto susceptibility testing is not possible as there exists a discrepancy between the testing methods.[9] The breakpoint MIC value for Eto used presently was titrated much earlier and there is a chance for the shift in breakpoint MIC value in context with the current scenario. The MIC obtained for INH in the study isolates were ≥ 5 µg/mL indicating the presence of dominant mutation due to the association of katG gene which has no association with Eto resistance.[2,4] Mechanism for resistance to ethionamide has still not been fully deciphered and involves more than one gene in development of resistance.[4] Recently, mechanism based on *msh*A gene indicates a possibility of non-INH induced Eto resistance, where insignificant association between susceptibility pattern of INH and Eto is expected.[10] Hence genetic characterization of ethionamide resistance is essential to determine cross resistance with INH.

To conclude, re-evaluation of breakpoint MIC and an accurate test for identifying Eto susceptibility profile should be addressed. Cross resistance between Eto and INH should be referred to in context to level of INH resistance. The molecular analysis of genes conferring resistance to Eto and INH especially the *inh*A gene and its promoter, might explain the role of INH in mediating cross resistance towards Eto.


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***Table 1. Drug susceptibility pattern of* Mycobacterium tuberculosis *isolates***

| Drugs | | No. of isolates (%) | Total (%) |
|---|---|---|---|
| INH | Eto | | |
| R | R | 68 (39) | 137 (78) |
| R | S | 69 (39) | |
| S | R | 13 (7.3) | 39 (22) |
| S | S | 26 (15) | |
| Total | | 176 | |

R, resistant; S, susceptible; INH, isoniazid; Eto, ethionamide.

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