

IS RESISTANCE TO ETHIONAMIDE AN EXTRAPOLATION OF OTHER FIRST AND SECOND LINE ANTI- TUBERCULOSIS DRUGS?

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ABSTRACT: Drug Susceptibility profile of ethionamide and other first and second line anti tuberculosis drugs revealed no significant association, indicating the resistance towards ethionamide is the result of individual effect and not an extrapolation of other drug resistant phenotypes.

KEY WORDS: Mycobacterium tuberculosis; MIC method; Ethionamide; Multi drug resistance

LETTER TO EDITOR:

Association of susceptibility profile between first and second line anti tuberculosis drugs was compared with ethionamide . Drug susceptibility profile of 134 pulmonary tuberculosis patients inclusive of new and previously treated were analyzed retrospectively. Results of conventional minimum inhibitory concentration (MIC) method for streptomycin (STR), isoniazid (INH), rifampicin (RIF), ethambutol (EMB), ethionamide (ETH), kanamycin (KAN) and ofloxacin (OF) were investigated. For reasons such as unavailability of results, susceptibility results not entailed or not possible due to contamination and cultures irretrievable for drug susceptibility testing (DST), drugs such as STR, EMB and KAN had

results available for only 72, 96 and 129 respectively. A total of 72 multi- drug resistant tuberculosis (MDR-TB), 62 non MDR-TB and six extensively drug resistant tuberculosis (XDR-TB) strains were observed (Table 1). Twenty eight (39%) MDR-TB isolates, exhibiting resistance to any one of the second line anti-tuberculosis drugs namely amino glycosides or fluoroquinolones were termed as pre XDR-TB in this study. Eighty three (62%) and 51 (38%) isolates were resistant and susceptible to ethionamide. Association between susceptibility profile of ethionamide and other anti-TB drugs tested were statistically insignificant. Role of EMB and KAN resistance with respect to ethionamide susceptibility needs to

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be re-assessed as there exists only limited KAN resistance among our population (data not shown) and DST for EMB is unreliable. Ethionamide and EMB are associated with cell wall biosynthesis directly or indirectly in *Mycobacterium tuberculosis*¹. In a way it could be a pseudo effect of altered or hindered metabolic pathway that is depicted as resistance. Resistance towards OF was reported to be as high as >50% by Ranjani et al (2009) from surveillance study conducted in the state of Gujarat². Since our study isolates form a part of the former study, association between OF and ETH susceptibility observed among the isolates may not be a true scenario. Conditions like MDR, non-MDR and XDR were also not found to be associated with ETH resistance. Due to the presence of high OF resistance, a slight increase (68%) in percentage of pre-XDR among ETH resistant isolates was observed. There is a speculation about INH and ETH susceptibility, where INH susceptible or low level resistance has a tendency to exert ETH resistance as these drugs are structural analogues and share similar mechanism of activation, action and target^{3,4}. Susceptibility profile of INH was designated as resistant, susceptible and borderline and compared with ETH susceptibility⁵. Difference in INH susceptibility was observed only within ETH resistant and susceptible isolates. Almost equal distribution of INH resistance was seen among ETH resistant and susceptible isolates and similar results were also observed with INH susceptible isolates. Isolates with borderline (BL) resistance to INH was observed in either category and was higher in ETH resistance. These isolates possess altered target which causes a constraint to the drug to bind at the active site thus evading drug action leading to resistance. Mutations in *inhA* gene responsible for INH-BL resistance, was found to have strong association with ETH resistance^{4,6}. Distribution of INH-BL isolates among ETH resistant as well as in susceptible isolates indicate that there could be other mechanisms causing resistance towards ETH. New

drug targets and mechanism of inhibition by ETH such as, eth operon consisting of *ethA* and *ethR* genes, *mshB* in mycothiol synthesis and *nudC* gene in nucleotide breakdown pathway has been identified⁷⁻⁹. With all the above reasons, it can be concluded that susceptibility towards ETH is not an extrapolation of resistance exerted due to other drugs used in treatment but could have been due to individual effect. But extrapolation of INH resistance leading to ETH resistance should be studied very carefully and addressed at molecular level.

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