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ETHIONAMIDE IN MDR TB: THE FALL OF A LEGEND

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The prime focus of this small review article is about an anti-tubercular drug which in-spite of being a well-known and good second line bactericidal drug against multi-drug resistant (MDR) strains of Mycobacterium Tuberculosis (MTB) has been relegated amongst the last but second of the Group C drugs in the current WHO recommended Classification of drugs for designing a Multi Drug Resistant (MDR) TB regimen. We now discuss this startling fall of a legendary anti-tubercular drug in the arsenal against fighting the scourge of MDR TB.

As per WHO recommendations, based on efficacy, tolerability and hence preference in adding sequentially, the second line drugs have been reclassified in three groups- A, B and C. Group A consists of the most effective drugs namely Bedaquiline, Moxifloxacin and Linezolid which should be first included while Group B comprises the drugs Clofazimine and Cycloserine which should be included in regime after Group A drugs. Included in Group C are the drugs which are included in sequence mentioned to complete the regime if Group A and Group B have been included and still a robust regime of at least 4 to 5 effective core of drugs is not being made. These drugs are Ethambutol, Delamanid, Pyrazinamide, Carbapenems, Amikacin (or Streptomicin), Ethionamide (ETH)/Prothionamide (PTH) and Para-amino salicyclic acid (PAS) (1).

ETH belongs to the family of medicines called thioamides and exerts its therapeutic action by the inhibition of Mycobacterial Fatty Acid Synthesis which is essential in the synthesis of the Mycobacterial cell wall. PTH is also a thioamide and it is firmly believed that both ETH and PTH share complete cross-resistance and virtually

interchangeable. ETH and PTH are also structural Analogues of Isoniazid (INH).

ETH has been an integral part of regimens in treatment of MDR TB from the beginning. It is also an integral part of the intensive phase (4-6 months) of the WHO recommended Short Course Regimen (Total Duration 9-11 months for Treatment of MDR TB with no additional resistance to FQ and Second Line Injectable (SLI) in patients who have not taken 2nd line drugs before or have taken them for less than 1 month. The WHO short course regimen was introduced after the results of the Bangladesh trial (2).

In spite of the very promising results of this trial, the WHO short course regime has not shown such good results probably because of improper patient selection and amplification of initial resistance to Fluoroquinolones (FQ) (3). The Bangladesh Trial used PTH whereas the WHO short course regime comprised of ETH. At one thought, it should not matter. For generations the TB specialists have considered the two drugs totally interchangeable. However, ETH has a very poor gastro-intestinal tolerance. It is one of the most unpleasant drugs to take and Clinicians treating MDR TB are only too aware of the notoriety of ETH in terms of Patient Compliance.

However, almost all programmes have used ETH and not PTH. The success of a regime depends not only on the efficacy of the drugs but also on their tolerability which affects patient's compliance with treatment and thus finally the outcome is also affected if compliance is poor. A search of the Literature brings up some evidence from very past studies (all done before the 1970) which lend some credibility to the possibility of PTH having a better gastro-intestinal profile than ETH (4), (5), (6).

This difference of tolerability between ETH and PTH may have contributed to the success of the Bangladesh regimen which utilized PTH. Another hypothesis for the success of the Bangladesh Regime may have been the use of Gatifloxacin instead of Levofloxacin or Moxifloxacin as there is some evidence to support the role of Gatifloxacin as better than Moxifloxacin or Levofloxacin in MDR TB (7). However, further discussion of FQ in MDR TB is beyond the scope of this review.

As mentioned above, ETH is a structural analogue of INH and both require activation in the body to exert their therapeutic effect which is again inhibition of mycolic acid synthesis of the Mycobacterial Cell Wall. The mechanism of INH resistance is multifactorial but the main mutations causing resistance to INH is KAT-G mutation which is most common. This mutation confers high level resistance to INH which means increasing the dose of INH will not overcome the resistance. However, patients with this mutation are likely to be sensitive to ETH if they have not received it before. However, in a proportion of patients, INH resistance is due to inh-A mutation which confers low level resistance to INH i.e. the patient will respond to high dose of INH but may be cross-resistant to ETH. Sharing a common biochemical pathway linked to the inhA gene is probably the reason for this cross-resistance. The frequency of these mutations is lesser but greatly varies depending on geographic location.

In general, KatG mutations tend to be more frequent (42–95% of isolates), while inhA mutations occur in 6–43% of isolates; around 10% of M. tuberculosis isolates have both mutations with both high and low levels of INH resistance and thus may also be cross-resistant to ETH (8).

Rapid molecular tests as Cartridge-based Nucleic Acid Amplification Tests (CBNAAT) give Rifampicin resistance in hours but for INH resistance, we need Line Probe Assay (LPA) which requires a lot of manpower and infrastructure. If treatment is started without knowing INH resistance, inhA

mutation will be missed and ETH in the regime will also be resistant leading to unfavorable outcome and failure.

As mentioned above, cross-resistance pattern of ETH and INH may show geographic variations sometimes to extremely high levels (~ 90%) due to much higher prevalence of inhA mutation in certain countries in the world such as Brazil and Korea (9) (10).

Now we address the basic question again-why has ETH been placed so down in the list of second line anti-tubercular drugs. We argue this point by asking another question? Why has Cycloserine (CYC) been placed so high in the armamentarium of second line ATT? CYC is only a bacteriostatic drug and is associated with serious neuro-psychiatric effects. Then why this role reversal? Two qualities of CYC which are its boon are, firstly an excellent gastro-intestinal tolerability and secondly the absence of any known cross-resistance to any other class of second line drugs (11).

As the above statement shows, the very lack of the aforementioned qualities of CYC are now the bane of ETH which are, firstly, A very poor gastro-intestinal tolerability and secondly, an unpredictable cross-resistance with INH, one of the most important first line Anti-tubercular drugs. ETH also has cross resistance with Thioacetazone but the latter is no more recommended in the treatment of either drug sensitive or drug resistant TB because of the highly increased risk of potentially fatal cutaneous adverse effects especially Toxic Epidermal Necrolysis and Stevens-Johnsons Syndrome in HIV-infected patients (12).

In conclusion, it can be presumed on our part that by now the reader can truly understand why a very good second line drug in MDR TB, is after all not so good any more. But the fact remains that ETH is still a very effective anti-tubercular drug if cross resistance to INH can be ruled out by gene analysis and PTH may be tried in such patients who are susceptible to the drug but are having gastric side effects which may jeopardize compliance as well as a favorable Outcome not because of its efficacy but due to its toxicity.

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