Letter to the Lancet

Sir,

In their review article ‘Programmes and principles in treatment of multidrug-resistant tuberculosis’, Joia S Mukherjee et al. recommend the use of at least 5 drugs to which the Mycobacterium isolate is sensitive (1). They do not specify, however, when an isolate should be considered to be resistant to an anti-tuberculosis drug. In our opinion, it remains unclear when isoniazid (INH) in particular should be left out of an anti-tuberculosis regimen because of resistance.

The World Health Organisation (WHO) recommends a Minimal Inhibitory Concentration (MIC) of > 0.2 μg/ml as cut-off point for isoniazid resistance. A study in mice, however, showed that the use of INH was useful in the treatment of a Mycobacterium tuberculosis infection caused by low level INH-resistant organisms (MICs between 0.2 and 5 μg/ml) (2). Clinical data are controversial but certain cohort studies suggest that continuing INH in a treatment regimen for patients infected with an INH-resistant strain may be beneficial (3).

INH is a low cost drug and is the antituberculosis drug that penetrates best into the central nervous system. Therefore, particularly in countries with limited resources where access to second line antituberculosis drugs is limited, and in regions with a high prevalence of disseminated and central nervous system tuberculosis due to HIV-induced immunosuppression, there is an argument for quantifying the level of INH-resistance before omitting INH from the treatment regimen. One of the minimum conditions for
establishing a WHO-supported DOTS-Plus pilot project for the management of MDR-TB is a local laboratory network in which drug-susceptibility testing for first-line anti-TB drugs can be performed. We propose that when INH resistance testing is performed, at least 2 INH concentrations should be determined (0.2 and 5 µg/ml). This is feasible without extra training and with a minimal investment in laboratory equipment.

A study in South Africa showed that the MICs of INH for approximately 50% of the INH resistant organisms were between 0.2 and 5 µg/ml (4). In a study of INH resistant strains in Ethiopia, the MIC of isoniazid was less than 4 µg/ml for 28 (70 %) of 40 strains (5). The eventual return for using a low price antituberculosis drug rather than a more expensive second line alternative could be substantial.

We agree with Joia S Mukherjee et al. that controlled clinical trials are needed to define optimal treatment regimens for MDR-TB. We suggest that such trials should also evaluate the usefulness of including INH in treatment regimens for Mycobacterium tuberculosis strains with low level INH resistance.

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