Chronic cough

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Lung alert

Pharmacological manipulation of antituberculous therapies to improve treatment efficacy and compliance with ethionamide

The global multidrug-resistant tuberculosis epidemic has prompted efforts to develop new antimycobacterial compounds and strategies to improve efficacy and compliance of drugs already in use. Several antituberculous compounds require in situ metabolic activation to become inhibitory to the mycobacterium. Ethionamide, a thiocarbamide-containing drug, is activated by the mycobacterial mono-oxygenase EthA. The production of EthA is inhibited by the transcriptional repressor EthR.

This study investigated the use of inhibitors of EthR to boost activity of EthA, thus increasing the efficacy of ethionamide. The ligands BDM31381 and BDM31343 were identified as compounds that inhibit EthR in vivo, resulting in increased activity of EthA. The minimum concentrations of ethionamide needed in the presence and absence of both ligands showed that BDM31343 and BDM31381 increased the antibacterial potency of ethionamide towards *Mycobacterium tuberculosis* by factors of 10 and 20 respectively. BDM31381 also improved the potency of thiacetazone, another antimycobacterial compound, by a factor of 4. In vivo studies in mice infected with *M tuberculosis* showed that BDM31381 with ethionamide only had a minor effect on bacterial load compared with ethionamide alone, while BDM31343 with ethionamide reduced bacterial load as efficiently as a three times higher dose of ethionamide alone.

This study supports the hypothesis that the sensitivity of *M tuberculosis* to a prodrug can be increased by interfering pharmacologically with the regulatory mechanism of drug activation. This could result in lower drug dose requirements, improving side effect profiles and increasing compliance—a potential step forward in the fight against multidrug-resistant tuberculosis.

Willand N, Dirie B, Carette X, et al. Synthetic EthR inhibitors boost antituberculous activity of ethionamide. Nat Med 2009;5:537–44.

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