

Editorial

Mycobacterial Diseases

Thioridazine as an Adjunct for Therapy of Multi-Drug (MDR), Extensively Drug Resistant (XDR) and Totally Drug Resistant (TDR) Pulmonary Tuberculosis Infections

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Pulmonary tuberculosis (TB), once thought to be on track for complete elimination during the 1950's as a consequence of improved social conditions, delivery of public health, diagnosis and therapy with the two most effective anti-tubercular agents Isoniazid (INH) and Rifampicin (Rif), has, as a consequence of social and political strife which reduced or reversed the positive trends of the 1950's, returned with a vengeance. And because of the large migrations of peoples from where the resurgence of pulmonary tuberculosis took place, the countries and cities that received these migrants also have experienced a huge resurgence of TB [1]. However, although therapy of pulmonary TB is almost always successful with INH and Rif, poor delivery of therapy has resulted in the selection of mutants that spontaneously arise from the prolonged period of therapy, and these are immune to the effectiveness of INH and Rif. This resistance is termed MDR TB and although the recent World Health Organisation Report suggests that the increased frequency of global MDR TB has for the first time plateaued [2], the fact that faithful and accurate reporting by countries such as India which has the largest population of pulmonary TB and MDR TB in the world, is suspect, and in all probability, MDR TB continues to increase globally [3]. And because MDR TB under the best circumstances is problematic for therapy, the increase of global MDR, in effect, is expected to continue. The problem with MDR TB infections has now progressed to a further level of resistance which is termed extensive drug resistance (XDR). XDR TB is resistant to INH, Rif, to any quinolones, streptomycin, and any of the intravenous anti-TB drugs amikacin, capreomycin and kanamycin. If this highly pulmonary TB infection is worrisome, there is now increasing evidence that the MDR phenotype of the infectious agent Mycobacterium tubeberculosis (Mtb) has progressed to a level which is termed "totally drug resistant TB (TDR TB) [4]. The very serious question is "What can be done to successfully treat MDR, XDR and possibly TDR pulmonary TB patients given that the available armamentarium of anti-TB drugs is not totally effective for therapy of MDR TB, not effective for therapy of XDR TB and certainly, if the term XDR TB is appropriate, irrelevant for therapy of XDR TB. Fortunately, there is an old drug that has been used for over 35 years to treat psychosis, which when used correctly and with care, produces no harm [5], and which when used in combination with certain anti-TB drugs, has the potential to cure the TDR TB patient [6]. This neuroleptic is thioridazine (TZ) a compound indirectly derived from the first neuroleptic chlorpromazine (CPZ). TZ has been shown to inhibit the in vitro replication of all studied strains resistant to INH and Rif [7,8], to enhance the killing of intracellular MDR TB [9] and XDR TB [10] by non-killing human macrophages, to cure the infected mouse of antibiotic pan-sensitive strains of Mtb [11] and MDR Mtb strains [12] and now, it has been shown to cure XDR TB patients when used in combination with antibiotics to which the strains were initially resistant [13]. Although the precise mechanism of intracellular action is not yet determined, a large bulk of evidence has been provided which suggests that the compound is concentrated by the human macrophage [14] to a level which results in the inhibition of replication comparable to that demonstrated in vitro [7,8]; that the compound inhibits the efflux pumps of the MDR Mtb strain responsible in part or completely for the mdr phenotype of the strain [15]; and, that by inhibiting the efflux of potassium from the phagolysosomal prison of Mtb, the acidification of the this vacuole takes place resulting in the activation of the hydrolases which degrade and kill the bacterium [16]. This many-fold mechanism of action insures that unlike the response of the organism to an antibiotic, little possibility of resistance to the intracellular action of TZ is anticipated. Because TZ activates the killing machinery of the nonkilling human macrophage, a new concept for therapy of pjulmonary TB results: rather than aiming therapy at the infective agent which one always knows will result in resistance, therapy is aimed at activation of the killing machinery of the human macrophage [17] which evades the mutational response of the organism. The ability of TZ to inhibit the microbe's over-expressed efflux pump system which is partly responsible for its mdr phenotype, means that old and cheap and effective antibiotics such as INH can again be used in combination with TZ. Obviously, this alone is a huge boom for indigent countries where mdr Mtb infections are frequent and therapeutic attempts costly [18].

At the moment TZ is receiving serious attention given its prominence in recent reviews by others [19-23]. It is hoped that these and others that are in the "pipeline" will further stimulate studies and therapies with TZ as an adjunct to antibiotics for therapy of mdr infections of pulmonary tuberculosis. Lastly, as shown by the studies of Utwadia et al. when TZ is used with care, it will not cause harm [5] thereby obeying the sacred oath that a physician takes "..... above all else, do no harm."

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