

## Totally Drug Resistant Tuberculosis can be Treated with Thioridazine in Combination with Antibiotics to which the Patient was Initially Resistant

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Two weeks ago, Zarir Utwadia identified 5 patients of a Mumbai hospital that presented with tuberculosis caused by strains of *Mycobacterium tuberculosis* that were classified as “totally drug resistant” (TDR Mtb) [1]. Given that Mumbai has almost 13 million inhabitants, currently incurable TDR infections of tuberculosis pose a significant health problem, not only to India but to the world, since infectious diseases do not recognise borders.

The question of whether TDR TB infections can be currently cured by an alternative to current ineffective therapy is discussed in this editorial and the supporting evidence that indeed the use of an old neuroleptic phenothiazine drug will most like cure an TDR TB infection is presented.

Thioridazine is an old neuroleptic that replaced the first commercial neuroleptic chlorpromazine (trade name lactargil) inasmuch as the former produced fewer serious side effects than the latter. Thioridazine however, is not free of serious side effects. Albeit infrequently, it may produce prolongation of QT interval (time between heart beats), arrhythmia, tordade de pointes, and rarely, even sudden death [2]. However, with proper attention to these potential problems, cardiac monitoring prior to and during initial therapy with thioridazine is commenced at a low dose that is increased slowly, the drug is relatively safe when compared to other newer and more commonly used neuroleptics [2].

The *in vitro* antitubercular properties of thioridazine were first described more than 15 years ago [3] at the time that resurgence of tuberculosis and its multi-drug resistant forms of infection were noted world-wide. However, the concentrations needed to completely inhibit the *in vitro* replication of the organism were clinically irrelevant given that these concentrations were in the range of 25 to 30 mg/L and the maximum safe level that can be achieved in the patient is *ca.* 0.5 mg/L of plasma. Crowle et al. [4] had demonstrated that chlorpromazine enhanced the killing of intracellular *Mycobacterium tuberculosis* at a concentration in the medium that was in the range present in plasma of a chronically treated with this neuroleptic. Given that tuberculosis is essentially an intracellular infection, the question of whether thioridazine, the equal to chlorpromazine as an *in vitro* tubercular agent [3], has similar intracellular activity against multi-drug resistant *Mycobacterium tuberculosis*, was soon investigated and shown to promote the killing of intracellular multi-drug resistant *Mycobacterium tuberculosis* by non-killing human macrophages at a concentration that was close to that initially used to treat a freshly diagnosed case of psychosis [5]. Thioridazine has been shown to cure the mouse of an antibiotic susceptible [6] and multi-drug resistant [7] infections and most recently, shown to cure patients infected with extensively drug resistant strains of *Mycobacterium tuberculosis* when used in combination with antibiotics to which the patients were initially resistant [8]. When used as monotherapy, thioridazine has been reported to significantly improve the XDR TB patient’s quality of life and has been recommended to be used as a salvage drug for therapy of the XDR TB patient [9].

Why does thioridazine cure the XDR TB patient? Thioridazine, as

is true for most phenothiazines, inhibits efflux pumps of bacteria [10] and human cells [11] that when over-expressed render these cells multi-drug resistant. Inhibition of these over-expressed efflux pumps reduces or reverses resistance to antibiotics to which the bacterium is initially resistant [12]. With respect to the macrophage within which the organism essentially resides, killing is promoted by the inhibition by thioridazine of calcium and potassium efflux from the phagolysosome that has entrapped the bacterium. Because these ions are needed for the acidification of the contents of the phagolysosome [13,14], and acidification activates the hydrolytic enzymes which degrade the bacterium [13,14], inhibition of calcium and potassium efflux by thioridazine promotes killing by the non-killing human macrophage [15]. The enhancement of killing rather than targeting the microbe avoids any mutational response by the organism which normally takes place with the use of antitubercular drugs [16,17]. In addition to this aforementioned mechanism, over-expressed efflux pumps which contribute to the multi-drug resistant phenotype of *Mycobacterium tuberculosis* are also inhibited by thioridazine [18], thereby rendering the organism susceptible to antibiotics to which it was initially resistant. The effect of thioridazine on the efflux pumps of the macrophage and the bacterium is also assisted by the concentration of the compound by lysosomes of the macrophage [19]. Because the killing of the bacterium is independent of the antibiotic status of the bacterium, the use of thioridazine for therapy of the XDR and now, the TDR TB patient is expected to be successful. Given that unlike the life-long therapy of the psychotic patient, the use of thioridazine for therapy of these antibiotic resistant infections is expected to be in terms of months [8] rather than years, the negative side effects produced by thioridazine, albeit, infrequent, are expected to be far less frequent. Given that at this time, there are no drugs known to cure the TDR TB infected patient, and thioridazine when used as described herein is safe, and very cheap, it must at this time be considered for therapy of the XDR TB patient.

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