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Review Article

Thioridazine: a potential adjuvant in pharmacotherapy of drug- resistant tuberculosis

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ABSTRACT

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. Despite advances in control strategies, inadequate treatment and failure to comply with drug regimens have resulted in TB to emerge as one of the most common and deadly infectious diseases worldwide. The emergence of drug-resistant TB has evolved as a formidable obstacle for comprehensive TB control. Drug-resistant TB can be classified as multi-drug-resistant TB, extensively drug-resistant TB and totally drug resistant TB (TDR-TB). There is a paucity in the development of new drugs against drug-resistant mycobacteria. The focus has shifted to the exploration of anti-mycobacterial properties of drugs approved for other indications. Thioridazine, a drug approved for use in schizophrenia is one such potential agent, which has shown anti-mycobacterial activity. There is evidence of anti-mycobacterial action of Thioridazine in *in-vitro* and mouse models. There is a compelling need for new anti-mycobacterial drugs that are more effective and have less toxicity. Further clinical trials are advocated favoring the use of thioridazine as an adjuvant in the treatment of TB, especially TDR-TB.

Keywords: Tuberculosis, Drug-resistant tuberculosis, Thioridazine

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (Mtb). Pulmonary TB is the most common form of TB (more than 85% of all TB cases), while extra pulmonary TB can affect almost any organ in the body. If properly treated, TB caused by drug-susceptible strains is curable in virtually all cases. If untreated, the disease may be fatal within 5 years in 50-65% of cases. Despite advances in control strategies, inadequate treatment and failure to comply with drug regimens have resulted in TB to emerge as one of the most common and deadly infectious diseases worldwide.

According to the global TB report published in 2013 by the World Health Organization (WHO),[1] reported by 178 member states and a total of 197 countries and other territories, in 2012, an estimated 8.6 million people developed TB, 1.3 million died from the disease, which included 320,000 deaths among HIV-positive people. India has the largest total incidence, with an estimated 2.0 million new cases.[2] Moreover, there has been increased the incidence in multi-drug-resistant (MDR-TB) and extensively drug-resistant strains (XDR-TB) of Mtb. MDR-TB is defined as resistance to isoniazid and rifampicin, with or without resistance to other anti-mycobacterial drugs.[3] When MDR-TB has additional resistance to a fluoroquinolone and a second line injectable antibiotic (i.e. amikacin, kanamycin or capreomycin), it is designated XDR-TB.[3,4] The term "XDR-TB" was coined in 2006.[5] XDR-TB has advanced to totally drug resistant TB (TDR-TB) in some parts of the globe. TDR-TB was first reported in 2009 by Velayati et al.[5] in Iran. Later, such strains have also been reported in Italy[6] and recently in India.[7] Though TDR-TB has not been clearly defined by the WHO, it can be considered to be a form of TB that is resistant to all currently used drugs. Table 1 summarizes the various forms of TB and its resistance patterns.

Table 1: Drug resistant patterns in TB.

Drug class	MDR-TB	XDR-TB	TDR-TB
Isoniazid, rifampicin	Resistant	Resistant	Resistant
Pyrazinamide, ethambutol	Susceptible	Susceptible	Resistant
Fluoroquinolones (levofloxacin, moxifloxacin, ofloxacin)	Susceptible	Susceptible/resistant	Resistant
Injectable drugs (capreomycin, kanamycin, amikacin)	Susceptible	Susceptible/resistant	Resistant
Other second line drugs	Susceptible	Susceptible	Susceptible/resistant

TB: Tuberculosis, MDR: Multi-drug-resistant TB, XDR: Extensively drug-resistant TB, TDR: Totally drug resistant TB

To deal with the problem of various drug resistant forms of TB, several anti-TB drugs with high efficacy have been discovered in the last two decades. However, the emergence of MDR and extensively-drug-resistant TB has evolved as formidable obstacles for comprehensive TB control. Furthermore, there is a paucity of development of new drugs against mycobacteria. This could be predominantly due to the biological mechanisms of mycobacterial drug resistance and also the economic concerns chiefly owing to lack of market incentives. Hence, the focus has shifted to the exploration of anti-mycobacterial properties of drugs approved for other indications. Thioridazine, a drug approved for use in schizophrenia is one such potential agent, which has shown anti-mycobacterial activity. This review will focus on the potential use of thioridazine in the anti-mycobacterial therapy, an approach that may restore the activity of antibiotics and render the mycobacteria more susceptible to drugs.

Mechanisms of mycobacterial drug resistance

Drug resistance in Mtb can be attributed to intrinsic and acquired mechanisms.[8] Intrinsic drug resistance has been attributed to a combination of highly impermeable mycolic acid containing cell wall and an active drug efflux mechanism.[9,10] Acquired drug resistance is generally mediated through horizontal transfer by genetic elements, such as plasmids, transposons or integrons. In Mtb, acquired drug resistance is not through horizontal transfer but is caused mainly by spontaneous mutations in chromosomal genes, producing the selection of resistant strains during sub-optimal drug therapy.[8] Resistance to first-line antimycobacterial drugs, isoniazid, rifampicin, pyrazinamide, streptomycin, ethambutol, and second-line drugs (fluoroquinolones, aminoglycosides, ethionamaide, p-amino salicylic acid) is attributed to specific mutations in target genes or regulatory domains. Table 2 summarizes the mechanisms of drug resistance of various antimycobacterial drugs.

ROLE OF THIORIDAZINE IN DRUG RESISTANT TB

Thioridazine is a neuroleptic that belongs to the class phenothiazines. These are a class of compounds that were first discovered to have anti-mycobacterial properties when used as a neuroleptic drug in the treatment of psychiatric patients with TB in the 1950s.[11,12] It is derived by structural modification of the first neuroleptic chlorpromazine[13] Figure 1

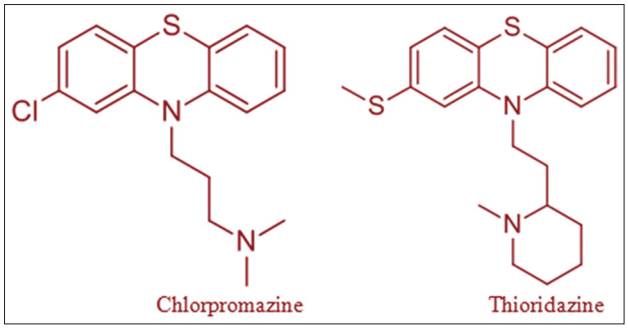

Figure 1: Chemical structures of chlorpromazine and thioridazine.

shows the differences between the chemical structures of chlorpromazine and thioridazine. The antipsychotic activity of thioridazine is mainly due to blockade of D_2 receptors.[14]

The mechanism through which thioridazine acts in drug resistant Mtb is by inhibition of efflux pumps of bacteria.[42] Over expression of efflux pumps contribute to development of drug resistant TB. Inhibition of these over-expressed efflux pumps reduces or reverses resistance to drugs to which the bacterium is initially resistant.[43] Active TB occurs when mycobacteria lyse the host cell, and prevent phagolysosome fusion by efflux of Ca^{2+} and K^+ ions and assembly of proteins that mediate phagolysosome fusion. Thioridazine also acts by inhibition of calcium and potassium efflux from the phagolysosome that has endocytosed the mycobacterium,[44] thus, enhancing the killing of intracellular Mtb by non-killing macrophages. In addition, it also inhibits Type II nicotinamide adenine dinucleotide: menaquinone oxidoreductase as a phenothiazine which is an intricate part of the aerobic respiratory chain of Mtb.[45]

Evidence of anti-mycobacterial action of thioridazine

The *in vitro* and *in vivo* activity of chlorpromazine against mycobacteria is well established.[46-50] The *in vitro* activity of thioridazine was also examined as it has a favorable toxicity profile relative to chlorpromazine. In a comparative *in vitro* study of phenothiazines against MDR Mtb by Bettencourt et al.,[51] the anti-mycobacterial activity of chlorpromazine and thioridazine were comparable. In another study by Amaral et al.[50] against a panel of Mtb strains that were resistant to as many as five antibiotics demonstrated that thioridazine is as effective in the inhibition of replication of Mtb as chlorpromazine. Table 3 gives the minimum inhibitory concentration (MIC_{50}) and MIC_{90}

Table 2: Anti-mycobacterial drugs and their mechanisms of drug resistance.

Drug	Gene	Target enzyme	References
Isoniazid	katG inhA ahpC	Catalase/peroxidase Enoyl reductase Alkyl hydroperoxide reductase	15-20
Rifampicin	rpoB	β-subunit of RNA polymerase	20-23
Pyrazinamide	pncA	Pyrazinamidase	20,24,25
Streptomycin	rpsL rrs gidB	Ribosomal protein S12 16S rRNA 7-Methylguanosine Methyltransferase	20,21,26-28
Ethambutol	embCAB	Arabinosyl transferase	20,21,29,30
Fluoroquinolones	gyrA/gyrB	DNA gyrase	20,31,32
Kanamycin/amikacin	rrs	16S rRNA	33-35
Capreomycin/viomycin	rrs tlyA	16S rRNA rRNA methyltransferase	34,36,37
Ethionamide	inhA ethA ethR	Enoyl reductase Flavin monooxygenase Transcriptional repressor	38-40
p-amino salicylic acid	thyA	Thymidylate synthase A	41

Table 3: MIC_{50} and MIC_{90} values of various phenothiazines.

Phenothiazine	MIC (mg/L)		
	MIC_{50}	MIC_{90}	Range
Chlorpromazine	4	16	<1-16
Thioridazine	4	16	2-16
Thioridazine enantiomer	8	16	4-16
Thioridazine, R-enantiomer	8	16	4-16

MIC: Minimum inhibitory concentration, $MIC_{50/90}$, MICs at which ≥50% and ≥90% of the isolates are inhibited, respectively

values of chlorpromazine in comparison with thioridazine and its enantiomers.[52] Although serum concentrations above the MIC for Mtb (8-16 mg/L range) are relatively high and clinically unachievable, thioridazine still has potential as an anti-mycobacterial drug because of intracellular accumulation, such that concentrations inside macrophages are at least 10-fold higher than in serum.[53]

Animal models have also revealed the activity of thioridazine against MDR-resistant Mtb. Van Soolingen et al.[54] demonstrated that thioridazine shows significant activity against drug-susceptible as well as MDR-resistant Mtb in a Balb/c mouse model. In another controlled study by Martins et al.,[55] the curative activity of thioridazine was studied by injecting high dose of the Mtb intraperitonially. The results of this study indicated that a daily dose of 0.5 mg/day of thioridazine reduced the number of colony forming units retrieved from the lungs of infected mice within 1 month.

Thioridazine has not been extensively studied in patients with TB. Of the few, a clinical study in Argentina by Abbate and his group has shown that thioridazine at doses of 25-200 mg/day can cure XDR-TB patient when used in combination with linezolid and moxifloxacin.[56] In another study on four Indian patients with XDR-TB, thioridazine was found to be well tolerated as salvage therapy with advanced disease.[57] Further trials are in progress to evaluate the potency, the safety profile of thioridazine in patients infected with MDR or XDR resistant strains of Mtb.[58]

CONCLUSION

The multifactorial mechanism of thioridazine against mycobacterium makes this a highly estimable drug in reversing drug resistance. However, its safety and therapeutic effects in TB remain to be further clarified given the ability of thioridazine to prolong the QTc interval. Therefore, further clinical trials are advocated for favouring the use of this indispensible drug as an adjuvant in the treatment of drug resistant TB, especially TDR-TB. In view of rapid emergence of drug resistant TB, there is a compelling need for the development of new anti-mycobacterial drugs that are more effective and have less toxicity.

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