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The added effect of thioridazine in the treatment of drug-resistant tuberculosis

The review by Grosset et al. in a recent issue of the *Journal* is highly interesting, and rightly pictures a bright horizon for the improved treatment of tuberculosis.[1] However, there are alternative compounds that can already provide considerable relief in compassionate application of treatment for multidrug-resistant and extensively drug-resistant tuberculosis (MDR/XDR-TB) in the short term, and may offer an important additional effect in treatment regimens due to a special working mechanism, such as efflux pump inhibition. The review did not, for example, discuss the successful use of the neuroleptic thioridazine (TZ) in MDR/XDR-TB treatment, although it has been widely examined and published. Our correspondence therefore addresses this omission and summarises in vitro, ex vivo and mouse studies of TZ, as well as the use of TZ in treatment of TB patients as monotherapy or as an adjunct in combination with drugs to which the causative *Mycobacterium tuberculosis* was initially resistant.

It has been known for many years that phenothiazines, and especially the traditional neuroleptic chlorpromazine (CPZ), possess in vitro activity against *M. tuberculosis*.[2] However, because the mode of action occurs at concentrations that are not considered tolerable in humans,[2] interest in CPZ as an anti-tuberculosis agent did not develop. Moreover, although these have been highly infrequent, the compound has been associated with serious side effects.[3] Nonetheless, with the emergence of MDR-TB in the late 1980s, CPZ regained interest as an anti-tuberculosis agent. In New York, new TB cases quadrupled during this period, more than half of these caused by MDR strains.[4] This re-emphasised the need for alternative treatments for TB, and at the time it was demonstrated that CPZ enhanced the killing of newly phagocytosed *M. tuberculosis* in human macrophages at clinically tolerable concentrations.[5] This observation regenerated interest in phenothiazines. Soon after, the milder phenothiazine, TZ, also showed considerable in vitro activity against all tested MDR-TB isolates.[6,7] Although the concentrations needed to inhibit the in vitro replication of MDR-TB isolates were still too high for clinical application, concentrations that enhanced the killing of newly phagocytosed MDR-TB bacteria were considered clinically tolerable,[8] revealing an important added effect of this class of drugs.

After in vitro studies, animal models are the next step in research on the efficacy of drugs. TZ appeared highly effective as a sole drug in the treatment of both susceptible[9] and MDR-TB in the Balb/C mouse model, and showed an added effect in combination with other drugs.[10] In the coming period, TZ and other drugs with a similar working mechanism, such as SILA421,[11] could be tested for their added value in treatment of TB in combination with the promising new drugs TMC207, PA824, PNU100480 or SQ109. In addition, higher dosages of rifampicin (RMP) are currently being tested in a drug trial in Tanzania and South Africa, and the utility of phenothiazines or similar drugs to acquire higher intracellular RMP concentrations at even lower dosage is worth exploring.

The recent report on totally drug-resistant tuberculosis (TDR-TB) from Mumbai exemplifies the urgent need for alternative treatments for TB; in the short term TZ may therefore be more important than realised.[12] Patients diagnosed with TDR-TB have already been exposed to virtually all available first- and second-line drugs without a favourable response, and physicians have run out of regular options. New TB drugs are therefore desperately needed to treat this category of patients. However, until the new drugs become available we will have to work with all drugs currently at hand.

Given the above, we first tested the safety and efficacy of TZ as salvage treatment in four Indian patients confronted with XDR (nearly totally) TB. We found it well tolerated and safe, even in malnourished patients who had failed treatment with all other drugs,[13] and we documented clinical and radiological improvement in three of the four patients.[13] In this small series, TZ was applied out of compassionate use, and treatment was started too late to achieve full bacteriological cure. Larger trials with TZ added on to standardised or individualised XDR-TB regimens at an earlier stage are foreseen. TZ has also been added to the salvage treatment regimens of three of the 15 cases of TDR-TB described by the Hinduja Hospital in Mumbai; these patients are also showing clinical, radiological and in two cases even a microbiological response.

Current drug choices for treating XDR- or TDR-TB are scarce. Information on the safety, tolerability and efficacy of alternative regimens is therefore of utmost importance. A retrospective study was performed among 17 adult pulmonary XDR-TB patients without the acquired immune-deficiency syndrome admitted to a referral treatment centre for infectious diseases in Buenos Aires, Argentina, from 2002 to 2008.[14] Drug combination schemes to treat these patients were tailored on the basis of drug susceptibility testing and the patient's drug tolerance. A combination of linezolid, moxifloxacin and TZ was applied in

the treatment of 12 of the patients. TZ was initially administered at a daily dose of 25 mg for 2 weeks, after which the dose was increased to 25 mg weekly until it reached 200 mg/day, under strict cardiac monitoring for eventual cardiac adverse events. Eleven patients met the recovery criteria with more than 2 years of follow-up after treatment completion. TZ was discontinued in one patient with pancytopaenia and in another with allergic dermatitis. Although cardiac adverse effects have been reported previously, no prolongation of QT interval or any other heart complication was observed.

The activity of TZ against the drug-resistant strain of *M. tuberculosis* that resides in the pulmonary macrophage of the alveoli is assumed to occur via two distinct mechanisms.[15] First, it enhances the killing of *M. tuberculosis* within the phagolysosome by inhibiting the cellular efflux of potassium, thereby promoting the acidification of the vacuole and activation of its hydrolases.[16] Second, because TZ inhibits the efflux pumps of mycobacteria, which are partially responsible for their resistance phenotype,[1] antibiotics that would normally be extruded by these efflux pumps because the intended target concentration cannot be reached are retained due to the inhibition of the efflux pumps by TZ.[2,17] Whereas the first mechanism avoids selection of mutated bacteria, the second mechanism ensures the effectiveness of the drugs when TZ increases the intra-cellular drug concentrations.

Treatment of TB is increasingly hampered by the emergence of anti-tuberculosis drug resistance. The rate of resistance is high not only in retreatment cases, but also in new, previously untreated cases.[18] This indicates transmission of resistant *M. tuberculosis* strains with presumably a higher level of intrinsic resistance to withstand exposure to drugs. The genetically conserved Beijing genotype strains have frequently been associated with drug resistance in the countries of the former Soviet Union and Asia. It was recently shown that some of these strains have elevated rates of RMP-resistant mutants,[19] and this may be a highly conceivable explanation for some of the resistance problems currently faced in these regions. However, in Europe also, the Beijing genotype in particular is associated with transmission of MDR/XDR-TB.[19] To combat the emergence of resistant TB, new drugs are in the pipeline. However, existing drugs, improved treatment regimens and more efficient dosages should also be explored in the short term to prevent morbidity and mortality. In particular, the synergistic effects of drug combinations have not been addressed sufficiently. TZ may have an added effect on the efficacy of all drugs due to its specific mode of activity, which yields higher intra-cellular concentrations of drug.

In conclusion, at the time of writing, only TZ has proven effective in the therapy of XDR-TB.[14] The adjunct use of TZ in combination with antibiotics to which the infecting organism was initially resistant is highly promising, and is recommendable out of compassionate consideration. In such cases, appropriate measures should be taken to limit or prevent any cardiopathy associated with TZ treatment, although the drug is generally safe to use.[13,14] In the USA, unsuccessful treatment of a single MDR-TB case can cost as much as $500 000,[20] whereas for a few hundred dollars an XDR-TB patient can be successfully treated with TZ. This drug should be considered in low-income regions of the world where the prevalence of MDR/XDR-TB is high. Moreover, because of its dual mechanism of action, TZ is expected to result in similar cure rates in TDR-TB patients.[21] A more scientific approach, with greater numbers of patients, should determine the true efficacy of TZ and similar drugs. This should not withhold the application of these drugs in compassionate use today.

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In reply

We are grateful to Drs Amaral et al. for their nice comments about our review on the new drugs for the treatment of tuberculosis (TB), and are pleased to respond to their comments about not having included thioridazine among the new drugs for TB. Let us remember that the objective of our review was 'to report evidence about the efficacy and potential of currently licensed drugs and new molecules beyond pre-clinical development for improving the chemotherapy of tuberculosis'. Thioridazine, an antipsychotic drug, is a piperidine belonging to the phenothiazine drug group. It replaced the first successful neuroleptic chlorpromazine (Largactil®), and was previously widely used in the treatment of schizophrenia and psychosis.[1] Its usual dosage was 50 mg per day for mild cases to 600–800 mg/day for severely disturbed patients. It was associated with cardiac and neuro-psychiatric side effects. The manufacturer Novartis/Sandoz/Wander of the thioridazine brands, Mellaril in the USA and Canada and Melleril in Europe, discontinued the drug worldwide in June 2005. Thioridazine may still be available from other manufacturers as a generic drug, with the precaution that it be used only in psychotic patients who are refractory to other forms of drug treatment.

The activity of the phenothiazines against *Mycobacterium tuberculosis* is fairly controversial. The minimum inhibitory concentration (MIC) of chlorpromazine for *M. tuberculosis* is 15–25 μg/ml, well above the maximum plasma concentration achieved in chronically treated humans, i.e., 0.5 μg/ml. Thioridazine has a similar MIC to that of chlorpromazine but, like chlorpromazine, is concentrated inside macrophages, and was demonstrated to have activity against *M. tuberculosis* in cell culture.[2] In the mouse infected with drug-susceptible *M. tuberculosis*, treatment for 32 and 70 days with thioridazine alone at daily doses of 32 and 70 mg/kg reduced the colony-forming unit (cfu) counts in lungs by 0.2–0.4 $\log_{10}$ compared with untreated controls. In the mouse infected with MDR *M. tuberculosis*, treatment with thioridazine alone at daily doses of 32 and 70 mg/kg reduced the cfu counts by 0.1–0.2 $\log_{10}$.[3] Anecdotal successes have been reported in humans with MDR-TB having received thioridazine-containing treatment on a compassionate basis.[1]

For all of these reasons, we did not, and we still do not think that thioridazine had to be included among drugs beyond pre-clinical development for improving the chemotherapy of tuberculosis.

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