Mitochondrial Metabolism Impairment and Ultrastructural Alterations Induced by Linezolid (LZD) and Tedizolid (TZD) at Clinically-relevant Concentrations: Studies with two human cell lines (HL-60 [Promyelocytes] and THP-1 [Monocytes])

Tamara Milosevic,1 Valéry L. Payen,2 Pierre Sonveaux,2 Giulio G. Muccioli,1 Françoise Van Bambeke,1 Paul M. Tulkens.1
1 Louvain Drug Research Institute and 2 Institute of Experimental and Clinical Research, Université catholique de Louvain, Bruxelles, Belgium

Abstract (edited and abridged)

Background and Aims

LZD inhibits bacterial protein synthesis. Due to the high degree of homology between bacterial and mitochondrial ribosomes, LZD also inhibits mitochondrial protein synthesis ([1-2]). Common unwanted effects of LZD (anemia, thrombocytopenia, lactic acidosis, nephropathy) are thought to result from impairment of mitochondrial protein synthesis and ensuing mitochondrial dysfunction ([3]). TZD shows lower MIC than linezolid due to the increased binding to bacterial ribosomes ([4]) and is also a more potent inhibitor of mitochondrial protein synthesis than LZD ([5]). However, TZD is effective and approved worldwide at a lower daily dose and short treatment duration (200 mg qD; 6 days) than LZD (600 mg BID; 10 days). The aims of our study were to compare TZD and LZD for (i) inhibition of the expression of a protein encoded by the mitochondrial genome, (ii) effects on mitochondrial metabolic activities and morphology in two types of cultured human cell lines (HL-60 [promyelocytes] and THP-1 [monocytes]) at microbiologically and clinically pertinent concentrations.

Methods

Both LZD and TZD cause an impairment of the expression of CYTox I, an inhibition of the activity of cytochrome c-oxidase, and a decrease of the spare capacity of the mitochondrial respiration in HL-60 and THP-1 exposed to concentrations pertinent of their mitochondrial activity and clinical use. TZD is globally more inhibitory than LZD even at microbiologically equivalent concentrations, potentially due to its higher intracellular accumulation (see above and [7]). Past recovery upon drug withdrawal, and once-daily regimen (5) combined with shorter treatment duration for TZD compared to LZD may mitigate its toxic effects in patients.

Typical Results (data expressed by reference to microbiological or human pharmacokinetic pertinent concentrations [see Methods])

Figure 1: CYTox I Western blot analysis (Tom20 as control)

Conclusion

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Background

Both LZD and TZD inhibit mitochondrial DNA-encoded protein synthesis causing mitochondrial dysfunction, which has been associated with the development of severe side effects (1-2). The objective of this study was to compare LZD to TZD for mitochondrial metabolism and ultrastructural alterations in human cell lines exposed to equivalent concentrations of these drugs.

Materials

HL-60 and THP-1 cells were tested for (i) oxidative metabolism using a mitochondrial membrane potential reporter (JC-1 assay, Becton Dickinson) and mitochondrial translocase of outer membranes (Tom20, ThermoFisher) and (ii) cytochrome c-oxidase activity (detection in HL-60, SchuS4 cytochrome c oxidase, mitochondrial space complex IV, ThermoFisher). Tom20, a mitochondrial DNA-encoded subunit of cytochrome c-oxidase, showed no detectable expression. Cytochrome c-oxidase activity, detected in human THP-1 cytoplasts and HL-60 cells, was significantly decreased in HL-60 cells exposed to 2.5 mg/L or 15 mg/L for LZD and 0.5 mg/L or 3 mg/L (Cmax) for TZD compared to controls. The biochemical effects were more pronounced in HL-60 than in THP-1 cells. The biochemical analysis was confirmed using different approaches (enriched in complex IV subunits: Cytox I and Cytox II). The effects of TZD were more pronounced than those of LZD in both cell lines. The biochemical effects were more pronounced in HL-60 than in THP-1 cells. The biochemical effects were more pronounced in HL-60 than in THP-1 cells.

Results

The recovery upon drug withdrawal, and once-daily regimen (5) combined with shorter treatment duration for TZD compared to LZD may mitigate its toxic effects in patients.