Tedizolid Inhibits Mitochondrial Metabolism and Reversibly Impairs Cytochrome c-oxidase Expression in Cultured Human Cells: Impact of a Discontinuous Exposure

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ABSTRACT

Background: Oxazolidinones inhibit mitochondrial DNA-encoded proteins (MNP), synthesized using mitochondrial ribosomes (mitr), and are thus required for mitochondrial respiration, cytoprotection, and autophagy. Our aim was to assess the potential of tedizolid (TZD), a more potent oxazolidinone, to inhibit mitochondrial metabolism when given intermittently.

Methods: Human THP-1 monocytes and HL-60 promyelocytes were tested for (i) lactate release (CMA 600 enzymatic assay using CMA600), (ii) mitochondrial protein expression (western blot of cytochrome oxidase subunit I (COX-I) and subunit II (COX-II)), and (iii) autophagy (increase in levels of lipidated microtubule-associated protein LC3). THP-1 monocytes were exposed to 3 or 0.5 mg/L for TZD, mimicking their corresponding human Cmax (total concentration). Results: TDZ causes MD in THP-1 monocytes (unactivated) with phagocytic capabilities. Continuous exposure (CT-dmso) to TDZ causes mitochondrial protein expression impairment. As drug wash-out allows for recovery, impairment of MD by TDZ when administered once daily may prepare to levels closer to normalcy. Lactate levels significantly increased after 48h of drug washing-out. The clinical impact may, however, be mitigated by the impact of cytochrome c-oxidase expression on mitochondrial metabolism. The clinical impact may, however, be mitigated by the

INTRODUCTION & AIM

• Oxazolidinones bind to ribosomes of both bacteria [1] and mitochondria due to a high degree of homology [2].
• In patients, TZD (the first approved oxazolidinone) causes myelosuppression [3], lactic acidosis [4] and neuropathies [5], all of which have been suggested to result from impairment of mitochondrial synthesis and ensuing mitochondrial dysfunction [6].

• Tedizolid (TZD) shows lower MICs than LZD due to increased binding to mitochondrial DNA-encoded proteins (MEP) synthesis, inhibiting mitochondrial metabolism when given intermittently [7]. However, TZD is approved for use at 0.25-0.5 mg/day only (Cmax) [8]. Whether mitochondrial metabolism when given intermittently could impair mitochondrial protein synthesis and expression of proteins encoded by mitochondrial genome is less known. In this study, we aimed at assessing the potential of TDZ (Cmax) to inhibit mitochondrial protein expression, mitochondrial respiration and autophagy, related to the expression of proteins encoded by mitochondrial genome, thus potentially impairing mitochondrial metabolism.

RESULTS

• Cells (human):
  • THP-1 monocytes (programmed of apoptosis and autophagy).
  • THP-1 monocytes (unactivated with phagocytic capabilities).

• Continuous exposure causes a complete impairment of COX-I expression.
• Transferring cells to fresh medium allows for complete recovery within 48h.

DISCUSSION AND CONCLUSION

In these in vitro models, tedizolid causes obvious mitochondrial metabolic impairment, probably related to the impairment of the expression of proteins encoded by mitochondrial genome. The clinical impact may, however, be mitigated by the fast recovery upon drug wash-out, especially if tedizolid is used for short periods and with a once-a-day schedule as recommended in the Prescribing Information.

REFERENCES

7. ZYVOX (available from labeling.pfizer.com/ShowLabeling.aspx?id=649)
8. Im (available from http://www.facm.ucl.ac.be/posters)

ACKNOWLEDGMENTS

This poster will be made available for download after the meeting at: http://www.facm.ucl.ac.be/posters