Oxazolidinone Antibiotics Reversibly Inhibit Mitochondrial Metabolism in Human Cell Lines

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Introduction

- Oxazolidinone antibiotics inhibit bacterial protein synthesis but also mitochondrial DNA-encoded protein synthesis (MEPS) in eukaryotic cells [1], which has been associated with the development of severe adverse effects (myelosuppression [2], lactic acidosis [3] and neuropathies [4]) upon prolonged treatments.
- Linezolid (LZD; approved in 2000) and tedizolid (TZD; approved by FDA in 2014 and EMA in 2015) are the two oxazolidinones currently on the market.
- TZD shows lower minimal inhibitory concentrations (MICs) towards susceptible bacteria than LZD due to increasing binding to bacterial ribosomes [5] and is also a more potent inhibitor of MEPS [6].

Aims of the study

- To compare the inhibitory potential of TZD and LZD towards the expression of a key protein encoded by the mitochondrial genome
- To assess its impact on mitochondrial respiration and metabolism in cultured human cells exposed to clinically-relevant concentrations of these drugs.

Methods

- Cells: Human promyelocytes (HL-60) and monocytes (THP-1)
- Mitochondrial protein expression: Western blot of cytochrome c-oxidase subunit I (CYTOX I) and succinate dehydrogenase (SDH), both encoded by mitochondrial and nuclear genome, with normalization using Tom 20 (outer membrane protein).
- Basal mitochondrial oxygen consumption rate (OCR) and reverse capacity: Seahorse XF96 bioanalyzer.
- Cytochrome c-oxidase activity: decrease of OD560 of cytochrome c.
- Autophagy: increase in level of lipidated protein LC3II (Western blot, normalized to actin) in the presence of leupeptin (cathespisin B inhibitor).

Treatments:
- Incubation with 2.5 or 15 mg/L for LZD and 0.5 or 3 mg/L for TZD (total concentration, corresponding to Cmin and Cmax in patients receiving approved daily dosages (LZD, 600 mg BID; TZD, 200 mg QD).

References


Results

1. Inhibition of CYTOX I expression (A) and cytochrome c-oxidase activity (B)

2. Changes in mitochondrial metabolism (basal respiration and reserve capacity)

3. Recovery of CYTOX I expression (A), cytochrome c-oxidase activity (B), and of mitochondrial respiration (C) in HL-60 cells

4. Autophagy (not illustrated)

Conclusion

Oxazolidinones cause mitochondrial metabolic dysfunction probably due to the impairment of the expression of proteins encoded by mitochondrial genome, which may explain the development of the severe side effects associated with their use.

In a biological context, oxazolidinones may stand as a useful tool to explore the metabolic and functional consequences of impaired mitochondrial protein synthesis.

Acknowledgments and Conflicts of Interest

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