Background

Solithromycin (SOL) is a novel fluoroketolide that shows enhanced potency, compared to other macrolides (e.g., azithromycin) against most susceptible strains and maintains low MICs against target organisms (e.g., Pneumococcus, respiratory tract, and skin/mucous membranes). In in vivo studies, solithromycin shows better efficacy against skin infections than azithromycin. Macrolides (e.g., azithromycin) are known to accumulate in the lysosomes of cells, and this effect of macrolides on cell metabolism and structure will be seen over the same period.

Methods

1. Subcellular distribution of SOL

- Collection of subcellular fractions
- Isolation of organelles
- Determination of drug content

2. Development of phospholipidosis

- Identification of phospholipid accumulation
- Measurement of lysosomal alterations

3. Lysosomal alterations at day 3 (microscopy)

- Visualization of cytoplasmic granules
- Electron microscopy

4. Reversibility of phospholipidosis, drug content, lysosomal alterations

- Reversal of phospholipidosis
- Drug content evaluation
- Lysosomal alterations

Main messages and conclusions

- SOL causes lysosomal phospholipidosis that is phenotypically and mechanistically lyosomal accumulation (this paper), impairment of phospholipidosis (A14) similar to what has been reported for azithromycin (2,7).
- N-acetyl-solithromycin causes a similar and CEM-214 less phospholipidosis than solithromycin. Generation of these metabolites is, therefore, unlikely to cause more alterations than what will be caused by solithromycin itself.
- In contrast to solithromycin, rapamycin is rapidly released from incubated cells with a constant return of total cell phospholipid content to its control value (for both SOL and NAS) and a large disappearance of the lysosomal alterations typically observed with azithromycin. This could mitigate against long-term toxicity of solithromycin in relation to phospholipidosis.

References

- Montenez et al. ToxicolAppl Pharmacol 1999;156:129-140. PMID 10198278
- Aubert-Tulkens et al. Lab Invest 1979;40:481-491. PMID 431047
- Solithromycin (SOL) is a novel fluoroketolide that shows enhanced potency, compared to other macrolides (e.g., azithromycin) against most susceptible strains and maintains low MICs against target organisms (e.g., Pneumococcus, respiratory tract, and skin/mucous membranes). In in vivo studies, solithromycin shows better efficacy against skin infections than azithromycin. Macrolides (e.g., azithromycin) are known to accumulate in the lysosomes of cells, and this effect of macrolides on cell metabolism and structure will be seen over the same period.

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