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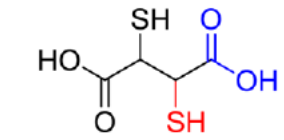
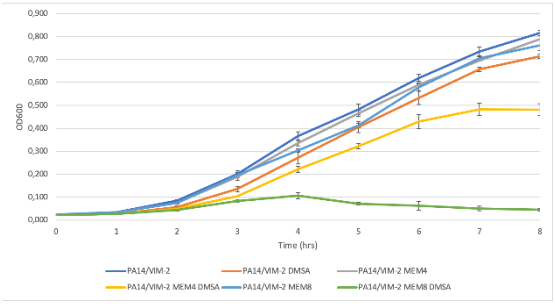
Meso-dimercapto succinic acid as an inhibitor of carbapenemases



Meso-2,3-
dimercaptosuccinic acid

Invention

Our *in vitro* studies show the inhibitory activity of DMSA against *Escherichia coli* and *Pseudomonas aeruginosa* producing the most frequent MBLs (NDM, VIM).



Killing curves *performed on P. aeruginosa PA14/VIM-2 in the presence of no antimicrobials, DMSA alone (3 mM), 4 and 8 mg/L Meropenem (MEM) alone, and DMSA (3 mM)/with MEM at 4 and 8 mg/L*

By using a peritonitis model of infection with an NDM-1 producer in *E. coli*, we showed that imipenem susceptibility may be recovered by addition of DMSA.

This invention takes the opportunity of using an already well-known molecule, DMSA, for inhibiting the activity of carbapenemases of the MBLs. This repurposing strategy may be a key of success for treating those difficult- or impossible- to-treat infections.

Summary

The proliferation of metallo-enzymes among Gram-negative bacteria poses a significant challenge by conferring resistance to carbapenems, leaving few therapeutic options. Meso-dimercapto succinic acid (DMSA), a heavy metal chelator, can restore carbapenem efficacy against metallo-ß-lactamase (MBL) producing bacteria. DMSA is very valuable asset in addressing antibiotic resistance within this context.

Background and current state-of-the-art

Multidrug resistance is dominated by emergence of carbapenemase-producing Gram-negative bacteria (*Enterobacterales, Pseudomonas aeruginosa* and *Acinetobacter baumannii).*
Among the carbapenemases, the MBL are the enzymes conferring the most resistance to antibiotics such as imipenem or meropenem which activity is not inhibited by inhibitors such as clavulanic acid, tazobactam, and avibactam. Efforts are underway to develop the aztreonam-avibactam combination, considering that aztreonam remains unaffected by MBLs. However, the emergence of aztreonam/avibactam-resistant strains, notably in community-acquired *Escherichia coli*, is rapidly increasing. This resistance is primarily attributed to modifications in the target of aztreonam, specifically the penicillin-binding protein 3

Fields of Application

- Antimicrobial resistance
- Treatment of infections associated with multidrug Gram-negatives infections
- *In vitro* identification of MBL producers

Patent Status

Patent filed and granted:
EP2979694A1

Publication

J Antimicrob Chemother 2020;75:3593-3600 and publication in progress concerning the in-vivo efficacy of DMSA against VIM-2 producer in *P. aeruginosa*

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