Contrasting Effect of Acid pH on the Bactericidal Activities of CEM-102 (Fusidic Acid) vs. Linezolid and Clindamycin Towards Staphylococcus aureus

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ABSTRACT

BACKGROUND AND AIM

Background. S. aureus is a widespread pathogenic bacterium showing high tolerance to pH variations. This confers an advantage for survival and colonization of body sites (see [1] for review) characterized by mild acidic pH, such as skin, vagina, urinary tract, or intracellularly, within the phagolysosomes of infected cells (pH = 5.0-5.5).

Acidity, however, may significantly decrease the activity of many antibiotics, as commonly observed for gentamicin (2) or azithromycin (3.4). In this context, we have compared the influence of acidic pH on the activity of CEM-102 (fusidic acid [a sterole-like antibiotic carrying a free carboxyl function]) vs. linezolid (LNZ) and clindamycin (CLI) towards S. aureus.

METHODS

Methods. S. aureus ATCC 25923 was grown in Mueller-Hinton broth (MHB). MICs were determined in MHB adjusted to pH 7.4 or pH 5.5. Dose-effect relationships at 24 h were examined for concentrations from 0.01 to 100 x the MIC. Results, expressed as the change in the inoculum at 24 h compared to time 0 h (T0), were used to fit a Hill equation to allow determination of the values of two key pharmacological descriptors of antibiotic activity (relative potency [EC 50; or 50% effective concentration] and maximal relative efficacy [Emax]; see Barcia-Macay et al, AAC 50(3):841-51).

RESULTS

Acidity did not affect bacterial growth (in the absence of antibiotic [E 0]) or [b] markedly decreased the MIC and the EC 50 of CEM-102. (ii) it had no effect on linezolid; and (iii) the EC 50 of clindamycin. Maximal relative efficacies (Emax) remained unchanged, with absolute values for CEM-102 similar to those of linezolid but lower than those of clindamycin. Conclusions. While maximal achievable efficacy is not modified, CEM-102 shows increased potency at acid pH. This may confer an advantage to this molecule for infections localized in low pH environments, such as skin, urine, or phagolysosomes of infected cells.

REFERENCES

(3) Lemaire et al. Antimicrob Agents Chemother (2009), In press

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