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MEETING ABSTRACT

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Fighting antibiotic resistance: the concept of mutant selection window and mutant prevention concentration

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Background: Appropriate antibiotic dosing is an important factor in preventing the emergence and proliferation of antibiotic-resistant strains. The mutant selection window (MSW) concept offers knowledge of the relationship between antibacterial pharmacodynamics and resistance development which is crucial for optimizing the use of existing antibacterial agents. It is based on a novel pharmacodynamic measure of antibiotic potency—the mutant prevention concentration (MPC). This review aimed to explore these concepts with regard to their clinical applicability.

Methods: A literature search (–2015) using the keywords 'mutant prevention concentration' or 'mutant selection window', and 'antibiotic' or 'antibiotics' or 'antibacterial' of the PubMed database.

Results: The search yielded 450 results and, after checking the titles, 181 abstracts; 84 articles were assessed in full text. The concept of MSW was first reported in 1999 in relation to fluoroquinolones. The basic concept is simple: within a susceptible bacterial population, a fraction of cells is not affected when exposed to an antimicrobial agent, and multiplication of this resistant subpopulation occurs in a range of concentrations (MSW) between the minimum inhibitory concentration (MIC) of the susceptible cells, and the mutant prevention concentration (MPC). MPC represents a concentration of antibiotic that prevents the development of first-step resistant mutants—the MIC of the least drug-susceptible mutant subpopulation. Multiple studies that monitored the increase in MIC after bacterial exposure to different concentrations of antibiotics confirmed that resistant mutants are selectively enriched when the antibiotic concentrations remain within the MSW. Besides on fluoroquinolones, this hypothesis has been tested in other classes of antibacterial agents such as polimixines, macrolides, aminoglycosides and beta-lactams *in vitro*. A limited number of studies tested these principles *in vivo*.

Discussion: Traditional dosing regimens often provide antibacterial concentrations within the MSW, allowing selective amplification of resistant mutants. Depending on the host defence mechanism, this leads to killing of susceptible bacteria and to a successful clinical response, but the possibility does exist that less susceptible microorganisms are selected. The MSW has been widely confirmed *in vitro*, but not all data generated *in vitro* agree with the results attained *in vivo*. The mutant selection window concept is definitely relevant for fluoroquinolones based on *in vitro* and *in vivo* experiments, but further research is necessary to determine the applicability of MSW *in vivo* for other antibacterial groups. For fluoroquinolones, MSW determined *in vitro* can be a reliable tool for guiding the optimization of antimicrobial treatment regimens for suppression of the selection of antimicrobial resistance, and clinical implementation of a selection window dosing strategy is feasible.

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