Clarification of MPC and the mutant selection window concept

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Keywords: antimicrobial resistance, mechanism, limitation

Sir, Smith et al.1 recently warned that the newly emerged mutant prevention concentration (MPC) concept has been stretched beyond its limits. The authors correctly caution that when MPC is measured in a way that does not reflect the major mechanism of clinical resistance, it cannot be used in the clinical setting: one cannot determine the number of oranges in a barrel by counting apples. However, the title of the article and the table presented may confuse or even mislead some readers. Thus, I’d like to clarify several key issues.

First, MPC is only an activity measurement; the concept is the mutant selection window. The selection window, first described for selection of particular resistant variants,2 is a drug concentration range within which mutants are selectively enriched. The MPC is the upper boundary of the window for all single-step mutants, not a subset.3,4 By maintaining antimicrobial concentrations above the window or by using proper drug combinations to close the window, pathogen populations are forced to acquire two concurrent resistance mutations for growth under antimicrobial therapy. Unfortunately, traditional dosing regimens often place drug concentrations inside the window such that a single mutation allows selective amplification of mutants. Choosing between the selection window approach and traditional strategies determines: (i) whether we stay two steps or only one step ahead of the bugs, (ii) whether we actively use the antimicrobial to attack mutants or rely only on host defences for that task, and (iii) whether we focus on suppressing the development of resistance or simply cure the majority of patients. These ideas should apply to a broad range of genetic resistance problems, not just those caused by quinolones and the like, as Smith et al.1 suggested.

Second, the selection window hypothesis is relatively insensitive to individual resistance mechanisms. Individual mechanisms mainly affect the first step in the development of resistance, the generation of resistant mutants, either through spontaneous mutations or through horizontal acquisition of foreign genetic elements. Little can be done to block the generation of resistant variants, since it is an intrinsic event. The selection window ideas address the second step, the selective enrichment of mutant subpopulations. Once a small fraction of mutants is present, the issue is whether they will be enriched, not how they came into being. Consequently, how a resistance-conferring element is obtained by a small number of pathogens before the enrichment step is largely irrelevant, which makes the selection window approach likely to apply to many types of resistance.

Third, a tight correlation between MPC and MIC for susceptible cells is not expected from the selection window hypothesis. If it were, the introduction of MPC as a measure for antimicrobial potency would be unnecessary. Indeed, MPC correlates much better with the MIC for the most resistant single-step mutant than with the MIC for susceptible cells.5 Correlation with lethal activity is also not expected, since killing is not a prerequisite for blocking mutant proliferation. Consequently, the selection window concept applies to agents that are not lethal.

Fourth, MPC determination can be modified to apply to resistance situations beyond those caused by spontaneous chromosomal point mutations (e.g. efflux, target alteration and derepression of inactivating enzyme production). For example, with horizontally transferred resistance, a small number of clinical resistant mutants can be added to a susceptible population for relevant MPC measurement. In the case of β-lactamase production, MPC may be determined with combinations of β-lactams and β-lactamase inhibitors.

Finally, the actual limitations for using the selection window concept to restrict antimicrobial resistance are quite different from those raised by Smith et al.1 First, when resistance is due to phenotypic induction or is caused by the so-called innate (primary) resistance, no enrichment is required for development of resistance. Consequently, these cases are outside the scope of the selection window idea. Second, complete reconstitution of a clinical setting for measurement of MPC, especially with horizontally transferred resistance, may be difficult because both susceptible and resistant clinical isolates are not isogenic. Third, if enzymic inactivation of a compound confers resistance to both the enzyme-producing cells and to surrounding, non-producing cells, determination of MPC becomes difficult because many susceptible cells may co-proliferate with resistant ones. Fourth, even though the selection window idea has been supported by a variety of in vitro studies and retrospective analysis of clinical cases, no animal data or human trials are available to test the hypothesis.

In summary, the mutant selection window hypothesis may have broad applications for fighting the growing problem of antimicrobial resistance. Although an easily measurable MPC or a well defined mutant selection window does not necessarily mean that an agent can be dosed above the window to suppress development of resistance, such measurements do provide guidance as to whether a compound can be used as monotherapy or whether it is better combined with another compatible compound.

References


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