Correspondence

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Overstretching the mutant prevention concentration

David M. Livermore*

Antibiotic Resistance Monitoring and Reference Laboratory,
Health Protection Agency, 61 Colindale Avenue, London
NW9 5HT, UK

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Sir,

Smith et al.1 make the good point that mutant prevention concentrations (MPCs, i.e. those drug levels that inhibit first-step mutants, mitigating against their clinical selection) are relevant only for antibiotic/organism combinations where resistance is mostly mutational, not for those where it usually involves species selection or DNA transfer. These authors do, however, underplay the role of mutational resistance, suggesting it is essentially restricted to fluoroquinolones. In reality, most resistance to β-lactams and aminoglycosides in Pseudomonas aeruginosa is contingent on mutations,2 as is most cephalosporin resistance in the Enterobacter, Citrobacter, Serratia group. Likewise, the initial emergence—though not the later spread—of TEM and SHV extended-spectrum β-lactamases entails mutation. In all these cases, the MPC has some potential relevance.

Perhaps a greater limitation than occasional misapplication is that the MPC’s proponents mostly consider only the target pathogen, and not other skin or gut organisms that are collaterally exposed, and which may be future opportunistic pathogens. Whilst (say) the concentrations of a new fluoroquinolone in respiratory secretions may exceed the MPC for pneumococci, this condition may not be met for skin staphylococci, exposed via the sweat, nor for gut Enterobacteriaeae, which are exposed to any unabsorbed antibiotic and to any that is excreted via the bile.

In short, the MPC should be seen specifically as a measure of the risk of mutational resistance being selected, during therapy, in the primary pathogen, not (as sometimes implied) as a general proxy for the ecological consequences of an antibiotic’s use.

References


Reply

Heather J. Smith1,2*, Daryl J. Hoban1,2 and George G. Zhanel1–3

1Department of Medical Microbiology, Faculty of Medicine, University of Manitoba, Manitoba; Departments of 2Clinical Microbiology and 3Medicine, Health Sciences Centre, Winnipeg, Manitoba, Canada

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*Correspondence address. Clinical Microbiology, Health Sciences Centre, MS673–820 Sherbrook St., Winnipeg, Manitoba R3A 1R9, Canada. Tel: +1-204-787-4684; Fax: +1-204-787-4699; E-mail: smithhj14@hotmail.com

Sir,

We thank Drs Livermore and Zhao for their provocative replies.1,2 Firstly, we thank Dr Livermore for his complimentary remarks.1 We agree that mutant prevention concentrations (MPCs) are only relevant for specific antibiotic/organism combinations in which resistance occurs as a result of mutational events. By focusing our discussion on fluoroquinolones,3 we did not mean to underplay the role of the occurrence of mutational resistance in other antibiotic/organism combinations, such as the β-lactams and aminoglycosides in Pseudomonas aeruginosa.

Dr Livermore raises concerns about the affects of antibiotic therapy on normal flora, such as the flora of the skin, pharynx and colon. We agree that MPCs evaluated for one antibiotic/organism combination cannot be extrapolated to explain resistance development in all organisms affected throughout the course of antibiotic therapy.

Secondly, we will address Dr Zhao’s statements.2 The sole focus of our paper was on the MPC: the antibiotic concentration above which an organism must acquire two resistance mutations for growth.4 The primary concern of our paper was that the MPC must only be applied clinically to situations studying the primary mechanism of clinical resistance. Dr Zhao states in his letter that he agrees with our concern.2 However, Dr Zhao introduces additional issues that were not discussed in our original paper, such as the mutant selection window (MSW) concept. This goes beyond the scope of our original paper. We intended simply to discuss the MPC as a potential dosing strategy and our concerns about the situations in which it is applicable. Subsequent to reviewing Dr Zhao’s comments, we still believe that the MPC and MSW pertain to the mutational resistance of a primary pathogen. The best current MPC model examines an organism/antibiotic combination in which a mutational event leads to a new phenotype, such that the organism survives in the presence of an antibiotic concentration that would have killed the organism prior to the mutation. The best documented examples involve the fluoroquinolones and Streptococcus pneumoniae or Mycobacterium tuberculosis.4,5 These are ideal situations for studying the MPC, as resistance develops in sequential mutational events. The current MPC and MSW data have only examined one antibiotic/one organism combinations. There are no data on how MPC measurements are affected in the...