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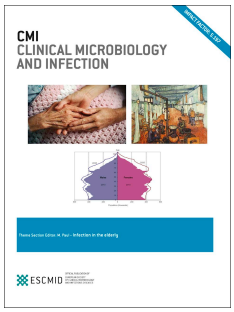

PK/PD characterization of combined antimicrobial agents: a real challenge and an urgent need

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PK/PD characterization of combined antimicrobial agents: a real challenge and an urgent need

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Pharmacokinetics (PK) concepts and methodologies have been developing extensively over the last decades and are now well mastered. By characterizing the Dose-Concentration relationship, PK allows precise description and prediction of drug concentrations profiles with time, mostly in plasma but also possibly within tissues at the infection site, and under various circumstances (doses, route of administration, age, pathology, drug-drug interactions). PK is partially responsible for the variability in drug effect. It varies quite extensively between patients and even within patients in the Intensive Care Unit setting and it is necessary to take into account this variability to avoid under or over dosage. Controlling drug concentrations is necessary but not sufficient to define the optimal dosage. This also requires a good understanding of the Concentration-Effect relationship that is pharmacodynamics (PD). And eventually the Dose-Effect relationship can be assessed by integrating PK (Dose-Concentration) and PD (Concentration-Effect) in order to define optimal dosing regimens.

In most therapeutic classes PK/PD integration relies on modeling approaches which allow precise predictions of the time course of effect even in complex settings, for instance when the drug PD is rapidly changing with time or/and in the presence of a front loading dose. But PK/PD modeling has only been used recently and on rare occasions to assess antibiotics PK/PD, which most often relies on minimum inhibitory concentrations (MICs) for PD characterization [1,2]. MIC is a static parameter that does not perform well to characterize antibiotic efficacy when concentration is changing with time. In order to cope with this difficulty, PK/PD indices such as Cmax/MIC and time over MIC have been considered, differentiating between concentration dependent and time dependent antibiotics. This approach has been accepted for long and has proven its usefulness for appropriate dosing of antimicrobial agents, but it is of note that such distinction between concentration and time dependent compounds does not exist in any other therapeutic classes and that it has limitations. The probability of reaching the target can be estimated (for example Cmax/MIC > 8 will be obtained in 85% of patients) but not the time course of effect, as can be done by PK/PD modeling (for example a CFU decay from 10^6 to 10^4 within 2 hours followed by a regrowth up to 10^7 after 6h).

PK/PD indices and targets have been extensively and successfully used for many years, however not in the context of combinations, whereas in practice several different antibiotics are often combined for the treatment of severe nosocomial infections, leaving important unanswered questions. As an example what would be the targets for a combination of two concentration dependent antibiotics with targets at Cmax/MIC>8 for each when given separately? A general tendency would probably be to consider that the best would be to keep the optimal dosing of each antibiotic administered separately. But there is no real scientific rational and no experimental support for that. Another more difficult question would be to define a relevant approach to assess and predict the net effect of combined concentration and time dependent antibiotics.