José Ramón Azanza Perea

The pharmacodynamic bases of the prescription of antimicrobials

Clinical Pharmacological Service – Clínica Universidad de Navarra

ABSTRACT

In the past, the dose of an antibiotic was chosen, always from among those that were well tolerated, by considering those with the ability to exceed the MIC of bacteria in plasma. This approach, which has still not widely changed, is contrasted with the pharmacokinetic and pharmacodynamic (PK/PD) relationships, which indicate that the efficacy of antibiotics is directly related to parameters that relate the sequence of concentrations over time with a parameter of the MIC effect *in vitro*. Until now, three types of PK/PD relationships have been established for antibiotics: the inhibitory coefficient (Cmax/MIC), the efficacy time (T>CMI) and the relationship between the exposure of the drug and the MIC (AUC/MIC).

Keywords: Antibiotics, PK/PD relationships

The gradual discovery of the importance of PK/PD relationships means that perhaps we will have to revise the posology of most anti-infectives. In the past, the dose of an antibiotic was chosen, always from among those that were well tolerated, by considering those with the ability to exceed the MIC of bacteria in plasma, in principle the higher the better. An identical approach was established for the choice of the administration interval, which was determined by considering how long the drug maintained concentrations in the plasma that exceeded the active infection. Sometimes, and considering possible problems of access to infected tissues, this meant adding to the above conditions the achievement of plasmatic concentrations that exceeded the MIC of the bacteria, throughout the posological interval by between 4 and 5 times.

Based on these premises, clinical trials are still designed during clinical research using posological guidelines that are often debatable. Therefore, in the field of daily practice, failures occur that are hard to explain and that could potentially have their origin, at least partly, in the lack of similarity between the patients included in clinical trials and the patients treated in health care practice, as the former are selected by following inclusion and exclusion criteria that are unrepresentative of the population where the antibiotics will be used in daily practice.

This approach, which has still not widely changed, is contrasted with the pharmacokinetic and pharmacodynamic (PK/PD) relationships, which indicate that the efficacy of antibiotics is directly related to parameters that relate the sequence of concentrations over time with a parameter of the MIC effect *in vitro*.

Until now, three types of PK/PD relationships have been established for antibiotics: the inhibitory coefficient (Cmax/MIC), the efficacy time (T>CMI) and the relationship between the exposure of the drug and the MIC (AUC/MIC).

The first of these indicates that the effect of a drug fundamentally depends upon the coefficient between the concentration reached and the minimum effective concentration. The drugs that belong to this group (aminoglycosides, colistin, nitroimidazoles and probably rifampicin) present greater activity *in vivo* the higher the administered doses are, without the administration interval being especially important. Consequently, it is recommended to administer the medicinal products in this group in one daily dose. The parameter that defines this relationship is the inhibitory coefficient (Cmax/MIC) and its ideal value appears to be greater than 10. In the case of aminoglycosides and considering the cut-off point of activity *in vitro*, this figure means that a dose of 7 and 20 mg/kg must be administered for gentamicin and amikacin respectively, a high dose that is potentially associated with a risk of renal and cochlear toxicity [1]. With colistin it has been indicated that the optimisation of its efficacy goes from the administration

Correspondence:
José Ramón Azanza Perea
Clinical Pharmacological Service – Clínica Universidad de Navarra
E-mail: jrazanza@unav.es

of a high loading dose of 9 MU, followed by a dose of at least 4.5 MU every 12 h, intravenously [2].

The second PK/PD model is mixed, as the parameters of interest are the concentrations achieved and how long they are maintained at values greater than the MIC, and consequently the AUC/MIC is the ratio that indicates the efficacy. The antibiotics belonging to this group must be administered in a dose that will generate the highest possible plasmatic concentration, and also at an interval that will avoid the presence of subinhibitory concentrations.

Fluoroquinolones are included in this section, the recognition of which has led to increasing the dose of levofloxacin and of ciprofloxacin [3]. In addition, vancomycin appears to be more effective when administered in regimes that reach AUC/MIC values that are greater than 400 (25,26), a situation that can pose therapeutic problems. Currently it is indicated that when the MIC of the causal strain of the infection is 2 mg/l, it is necessary to administer doses that are associated with nephrotoxicity [4]. In these circumstances it is necessary to verify the seric concentration of vancomycin in the valley immediately before administering the 5th dose (after reaching the state of stationary balance) and adjusting the following doses to obtain the desired values. In the case of linezolid, the optimum value of AUC_{0-24h}/MIC is 100, which means [5] that it is necessary to administer up to 3 daily doses in the case of strains that are within the cut-off point limit; 4 mg/L.

The best clinical response by daptomycin is achieved with AUC_{0-24h}/MIC >600 [6]. One dose of daptomycin of 6 mg/kg/day generates an AUC_{24h} of around 700 µg h/ml [7] which means an optimum exposure in the case of infection by methicillin-resistant *Staphylococcus aureus* (MRSA) strains with an MIC < 0.5 mg/l [8], but in the case of strains that present higher MIC values it is necessary to administer high doses that are usually 10-12 mg/kg/day.

The AUC_{0-24h}/MIC values of tigecycline that best discriminate between the probability of success or failure, clinical or microbiological, are 12 and 18 µg h/ml respectively [9]. With the usual dose of 50 mg/12 h iv, in a state of stationary balance, an AUC_{24h} in saline is obtained of 4-6 µg h/l, while the MIC_{90} against MRSA strains is 0.25-0.50 mg/l [10]. It is therefore usual to recommend the administration of double the dose.

The third of the models, which includes all β-lactam antibiotics, [11-13] seems to depend especially on maintaining free drugs above the MIC for as long as possible (T > MIC). This parameter, known as the efficacy time, is the reason for discrepancies, because some authors argue that it is not necessary that the estimate of the T>MIC to reach a value of 100%, that is, it might be sufficient for this value to be located at 40-50%. The real-life date provided by health care practice appears to oppose partial or interested readings and it is therefore increasingly evident that β-lactams must be administered at intervals that will cover the MIC of bacteria for as long as possible, that is, they must reach T > MIC = 100%. This result is simple for some drugs that have a very high elimination half-life, but complex in the case of antibiotics, which like the vast majority of β-lactams, present a plasmatic half-life of under 2 h. This is a difficult problem in p.o. administration and also in i.v. administration, which will require the administration of many daily doses or the use of another possible i.v. administration method, which is prolonged or continuous infusion [14, 15].

Logically, taking account of the storage and stability in solution conditions before making prescriptions of these types of infusions becomes a priority.

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