Individualized Dosing of Antibiotics in Asians Based on PK/PD

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Pharmacolinetics/Pharmacodynamics (PK/PD) of antibiotics offers the best science in antibiotic treatment for infections. Although MIC and MBC have been the major parameters used to determine the activity of antimicrobial agents for several decades, they provide only crude information on the time course of antimicrobial activity. The MIC approximates a continuous exposure of the drug for 24 hours at a threshold concentration. This approximate continuous infusion threshold may not reflect the relationship between the rate of killing microorganism and peak and trough concentrations of the antibiotic.

While pharmacokinetics of antibiotics deals with the time course of concentration of drug itself determined by absorption, distribution, and elimination, pharmacodynamics of antibiotics expresses the relationship between serum concentration of antibiotics and their antimicrobial effect. Described in this manner, pharmacodynamics of antibiotics focus on the time course of their antimicrobial activity.

Antibiotics with concentration-dependent killing and prolonged postantibiotic effect (PAE) such as aminoglycosides and fluoroquinolones are dependent upon peak level / MIC ratio and AUC (area under the concentration versus time curve) / MIC ratio for their antimicrobial efficacy. Antimicrobial activity of antibiotics characterized by minimal concentration-dependent killing and minimal PAE, such as β-lactams, is related with the duration of time above MIC (T > MIC).

Magnitudes of PK / PD parameters necessary for treatment efficacy also have been presented by a number of in vitro, animal model experiments, and a few clinical studies. For example, 24hr-AUC/MIC above 125 is believed to be the breakpoint to achieve favorable clinical

microbiological responses and 24hr-AUC/MIC above 250 is needed to achieve rapid bacterial killing. In case of vancomycin, it is accepted that 24hr-AUC/MIC above 400 should be the target PK/PD magnitude for positive clinical outcomes.

Knowledge about PK/PD parameters and their target magnitudes determining the effect of each antibiotic gives a hope to establish antibiotic treatment individualized to each patient. For example, 24h-AUC of antibiotics can be calculated by estimating the patient's creatinine clearance and using population clearance of drugs vs creatinine clearance equations. After estimating the patient's total clearance of candidate antibiotic, the total daily dose (mg/24hours) of the antibiotic can be divided by this clearance to derive the 24h-AUC. This AUC can then be divided by the MIC of the pathogen infecting the patient to estimate the 24h-AUC/MIC. If magnitude of the 24h-AUC/MIC is not appropriate comparing to the target magnitude, dose of the antibiotic can be adjusted to target appropriate 24h-AUC/MIC.

Individualized dosing of antibiotics has been tried by some scientists. Equations calculating antibiotic clearance by patient's creatinine clearance have been provided for several tens of antibiotics, especially for those excreted mainly kidney. Development of these equations is believed to make it possible to optimize antibiotic therapy by application of more scientific, more detailed, individualized dosing of antibiotics to each patient.

Until now, equations calculating antibiotic clearance have been obtained from western patients. In fact, drug clearance by creatinine clearance can be different by ethnic group because of their different fat distribution, different metabolism, genetic difference in drug transporting system etc. Therefore, individualized dosing of antibiotics by establishing drug clearance equations of each antibiotic also needs to be developed and validated in Asian countries. Our institution performed studies to develop drug clearance equations of some antibiotics in Korean patients and found that the equations are a little different from those derived from western patients. Those data will be presented soon and we are continuing further studies to get equations for individualized antibiotic treatment with other key antibiotics.