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Prespective

Target Controlled Infusion (TCI) of Beta Lactams may Enhance their Pharmacokinetic/Pharmacodynamic (PK/PD) Profile in Critically ill Patients

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Perspective

The management of infectious diseases in intensive care is becoming increasingly difficult for the continued rise of antimicrobial resistance. Given the lack of new antibiotics, the only chance we have to treat multiresistant pathogens is to maximizing the effectiveness of available drugs [1].

We know little of antibiotics pharmacokinetics and pharmacodynamics in critically ill patients.

Homeostatic disturbance, endothelial dysfunction, altered major organ blood flow, vasopressor medications, drug interactions, low plasma proteins concentration, organ dysfunctions, augmented renal clearance, use of extracorporeal circuits contribute to avert critical patients from healthy volunteers or other hospitalized patients, on which antibiotics pharmacokinetics were studied [2].

For time-dependents agents, such as ß-lactams and glycopeptides, *in vitro* and animal studies have demonstrated that the critical factor for bacterial killing is the amount of time in which the free drug concentration exceeds the MIC of the organism. So that we have to Maintain Sufficient drug Concentrations (>MIC) throughout the dosing interval.

To achieve this we have to tailor the dose to the Pharmacokinetic Characteristics (PK) of the patient, pratically we need to know the plasma concentration of antibiotic and set infusion programs able to reach the concentrations required.

De Waele et al. reported that Therapeutic Drug Monitoring (TDM)-based dose adaptation of ß-lactams improves antibiotic exposure in critically ill patients at risk of under dosing [3].

To reach elevated MICs we can administer the medication frequently or use continuous/extended infusions [4].

Recent meta-analysis concluded that continuous/extended infusions of antibiotics in critical patients improve cure rates and length of stay [4]. Additionally other studies showed that prolonged infusions are cost savings and mitigate the emergence of resistance.

Unfortunately, the plasma assay of antibiotics is not available in all hospitals and the implementation of TDM requires pharmacological expertise.

Enhanced knowledge of PK and PD would allow us to build Target Controlled Infusion (TCI)-devices for administering time-dependent antimicrobial drugs; as it does now for anaesthetics [5].

Target Controlled Infusion (TCI) is a computer-assisted administration of drugs designed to achieve a user defined concentration in a tissue of interest.

The computer is programmed with a pharmacokinetic model which is describing the distribution and elimination of the drug within the body. TCI-system calculates the initial loading dose needed to obtain the desired target concentration and the infusion rate needed to maintain it constant and sends instructions to the infusion device.

The clinician should decide the most appropriate antimicrobial and enter in the computer the desired target concentration and the clinical parameters of the patient.

The use of TCI-systems for antibiotics would get a target concentration continuously above-MIC, aim difficult to achieve with intermittent administration in critical patients infected by resistant pathogens.

A computerized system also would consider and weight all the pharmacokinetic changes that affect the critically ill.

Large-size studies on the Pharmacokinetics (PK) and Pharmacodynamics (PD) of time-dependent antibiotics in critically ill patients are required urgently to use them better and to give us the only weapon available in the short term against multiresistent pathogens.

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