THE ROLE OF PK/PD MODELS FOR OPTIMISING ANTIBIOTICS ADMINISTRATION IN CRITICALLY ILL PATIENTS WITH SEVERE INFECTIONS

JACOPO COLOMBO (ITALY)

KEYNOTE LECTURE – 17TH AUGUST 2018 8.30 – 9.00

Infection in critically ill patients

Infection is an important problem in critically ill patients and an important source of morbidity and mortality in intensive care units (ICUs)[1] .

Antimicrobial therapy has emerged as one of the most crucial elements in the treatment of severe infections and has been studied extensively in recent years.

Timely initiation of the antimicrobial agent as well as the selection of an antimicrobial agent with the appropriate spectrum have shown to be important determinants of clinical success.

In the Surviving Sepsis Campaign (SSC), treatment strategies are split into different bundles depending upon how immediately the treatment is required. Fluid resuscitation, oxygen therapy and antibiotics are in the 1 h bundle.[2] Antimicrobial therapy in critically ill patients most often is based on standard dosing protocols, with little or no attention to the baseline characteristics (e.g. weight) or the altered physiology of the patient that results in changes in pharmacokinetics (PK).[3]

Deciding on the dose of antibiotic in a septic patient is probably equally important to the timing.

Robust data are available for exposure effect relations between antibiotics and bacterial killing in vitro and in animals, but the effect of antibiotic exposure on mortality has not been well defined yet.[4]

Results from a randomised controlled trial with aminoglycosides showed that a dedicated therapeutic drug-monitoring intervention (also described as therapeutic drug management) in a general patient cohort in one hospital significantly reduced their length of stay.[5] Retrospective studies of quinolones[6;7], β lactams[6;8;9], glycopeptides[10] and linezolid[11] show advantages in terms of clinical cure, mortality, or both, associated with achievement of target pharmacokinetic/pharmacodynamic indices.

Altered antibiotics' pharmacokinetics in critically ill

Information about effective antibiotic dosing specifically for critically ill patients is not usually included in treatment guidelines; product information for the antibiotic usually guides the choice of dose for such patients.

However, product information is based on dose finding studies in patients who are not critically ill, and the results are then extrapolated to critically ill patients.

Increased volume of distribution, changes in protein binding and in the elimination rate from the circulation through the kidney or the use of extracorporeal circuits contribute to this substantial pharmacokinetic difference.[3]

Furthermore numerous studies have demonstrated that antibiotic plasma concentrations—especially those of hydrophilic antibiotics, such as β lactams—are variable and unpredictable in ICU patients.[12-15]

Consequently, general dosing guidelines for critical patients might not be a satisfactory solution16: pharmacokinetic variability reduces the ability to predict therapeutic doses of antibiotic for individual patients.

Multidrug-resistant (MDR) bacteria

In addition to pharmacokinetic problems, critical patients are often infected with bacteria with reduced antimicrobial susceptibility (that is pathogens with higher minimum inhibitory concentrations).[17]

The phenomenon of Multidrug-resistant organisms (MDR) is ubiquitous: three-quarters of European countries have reported at least one extensively drug-resistant organisms in ICU patients.[1] This is consistent with the continuously increasing trends of antimicrobial resistance and the high percentage of extended spectrum beta-lactamase (ESBL)-positive and carbapenemases-producing isolates.

A present and most worrisome problem is the emergence of panresistent isolates, for example colistin resistance in K. pneumoniae carbapenemase (KPC), involves in some countries up to 20 % of the isolates.[18]

It's important to underline that subtherapeutic concentrations of antibiotics may favour resistance development.

Antibiotics and critically ill: a difficult challange

To summarize: the critically ill patient with infection has 2 problems:

1. Physicians don't know how much antibiotic is necessary because critically ill patients are different from general populations in terms of drug absorption, distribution and elimination, on which dose finding studies were conducted, and have significant pharmacokinetic variability, so every critically ill patient is different from each other and effective dosing guidelines are difficult to write up
2. ICU infections are mostly due to MDR bacteria

A significant number of patients therefore have reduced antibiotic exposure and do not reach the pharmacokinetic/pharmacodynamic (PK/PD) target required for the treatment of severe infection.[3]

Treatment failure, worst outcome, increased length of stay, costs and selection of resistant organisms are the consequence of this failed goal. [6]

Pharmacokinetic/pharmacodynamic (PK/PD) targets

Optimisation of antibiotics dosing, such that predefined pharmacokinetic/pharmacodynamic (PK/PD) targets for maximal bacterial killing are achieved, has been proposed as one such approach to overcome these problems.[19;20]

Thus the major challenge for clinicians is to ensure that dosing achieves the pharmacokinetic/pharmacodynamic targets that are associated with improved likelihood of positive clinical outcomes.

The dosing strategy for antibiotics will vary depending on the mode of action of the drug and also on individual patient factors that influence its pharmacokinetic and pharmacodynamic (PK/PD) interactions.

References

1. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD *et al*. International Study of the Prevalence and Outcomes of Infection in Intensive Care Units. *Jama-Journal of the American Medical Association* 2009;**302**:2323-9.

2. Dellinger RP, Levy MM, Rhodes A. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012 (vol 41, pg 580, 2013). *Critical Care Medicine* 2014;**42**:E88.

3. Udy AA, Roberts JA, Lipman J. Clinical implications of antibiotic pharmacokinetic principles in the critically ill. *Intensive Care Medicine* 2013;**39**:2070-82.

4. Sime FB, Roberts MS, Peake SL, Lipman J, Roberts JA. Does Beta-lactam Pharmacokinetic Variability in Critically Ill Patients Justify Therapeutic Drug Monitoring? A Systematic Review. *Annals of Intensive Care* 2012;**2**.

5. Lent-Evers NA, Mathot RA, Geus WP, van Hout BA, Vinks AA. Impact of goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: a cost-effectiveness analysis. *Ther.Drug Monit.* 1999;**21**:63-73.

6. Scaglione F, Esposito S, Leone S, Lucini V, Pannacci M, Ma L *et al*. Feedback dose alteration significantly affects probability of pathogen eradication in nosocomial pneumonia. *Eur.Respir.J.* 2009;**34**:394-400.

7. Ambrose PG, Grasela DM, Grasela TH, Passarell J, Mayer HB, Pierce PF. Pharmacodynamics of fluoroquinolones against Streptococcus pneumoniae in patients with community-acquired respiratory tract infections. *Antimicrob.Agents Chemother.* 2001;**45**:2793-7.

8. Li C, Du X, Kuti JL, Nicolau DP. Clinical pharmacodynamics of meropenem in patients with lower respiratory tract infections. *Antimicrob.Agents Chemother.* 2007;**51**:1725-30.

9. Muller AE, Punt N, Mouton JW. Optimal exposures of ceftazidime predict the probability of microbiological and clinical outcome in the treatment of nosocomial pneumonia. *J.Antimicrob.Chemother.* 2013;**68**:900-6.

10. Zelenitsky S, Rubinstein E, Ariano R, Iacovides H, Dodek P, Mirzanejad Y *et al*. Vancomycin pharmacodynamics and survival in patients with methicillin-resistant Staphylococcus aureus-associated septic shock. *Int.J.Antimicrob.Agents* 2013;**41**:255-60.

11. Rayner CR, Forrest A, Meagher AK, Birmingham MC, Schentag JJ. Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. *Clin.Pharmacokinet.* 2003;**42**:1411-23.

12. Blondiaux N, Wallet F, Favory R, Onimus T, Nseir S, Courcol RJ *et al*. Daily serum piperacillin monitoring is advisable in critically ill patients. *International Journal of Antimicrobial Agents* 2010;**35**:500-3.

13. Aubert G, Carricajo A, Coudrot M, Guyomarc'h S, Auboyer C, Zeni F. Prospective Determination of Serum Ceftazidime Concentrations in Intensive Care Units. *Therapeutic Drug Monitoring* 2010;**32**:517-9.

14. Roberts JA, Kirkpatrick CMJ, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. *Journal of Antimicrobial Chemotherapy* 2009;**64**:142-50.

15. Roberts JA, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Piperacillin penetration into tissue of critically ill patients with sepsis-Bolus versus continuous administration? *Critical Care Medicine* 2009;**37**:926-33.

16. Taccone FS, Laterre PF, Dugernier T, Spapen H, Delattre I, Wittebole X *et al*. Insufficient beta-lactam concentrations in the early phase of severe sepsis and septic shock. *Critical Care* 2010;**14**.

17. Shorr AF. Review of studies of the impact on Gram-negative bacterial resistance on outcomes in the intensive care unit. *Critical Care Medicine* 2009;**37**:1463-9.

18. Giani T, Pini B, Arena F, Conte V, Bracco S, Migliavacca R *et al*. Epidemic diffusion of KPC carbapenemase-producing Klebsiella pneumoniae in Italy: results of the first countrywide survey, 15 May to 30 June 2011. *Euro.Surveill* 2013;**18**.

19. Udy AA, Roberts JA, De Waele JJ, Paterson DL, Lipman J. What's behind the failure of emerging antibiotics in the critically ill? Understanding the impact of altered pharmacokinetics and augmented renal clearance. *International Journal of Antimicrobial Agents* 2012;**39**:455-7.

20. Roberts JA, Ulldemolins M, Roberts MS, McWhinney B, Ungerer J, Paterson DL *et al*. Therapeutic drug monitoring of beta-lactams in critically ill patients: proof of concept. *International Journal of Antimicrobial Agents* 2010;**36**:332-9.

Declaration of Consent to Publication and Assignation of Copyright

☐ *I confirm that I previewed this abstract and that all information is correct. I accept that the content of this abstract cannot be modified or corrected after final submission and I am aware that it will be published exactly as submitted.*

☐ *Submission of the abstract constitutes my consent to publication (e.g. congress website, programs, other promotions, etc.)*

☐ *The Abstract Submitter warrants and represents that he/she is the sole owner or has the rights of all the information and content ("Content") provided to TIVA-TCI 2018*
The publication of the abstract does not infringe any third party rights including, but not limited to, intellectual property rights.
The Abstract Submitter grants the Organizers a royalty-free, perpetual, irrevocable nonexclusive license to use, reproduce, publish, translate, distribute, and display the Content:

☐ *The Organizers reserve the right to remove from any publication an abstract which does not comply with the above.*

☐ *I herewith confirm that the contact details saved in this system are those of the corresponding author, who will be notified about the status of the abstract. The corresponding author is responsible for informing the other authors about the status of the abstract.*