

Vancomycin Way of Administration: Where is the Evidence?

TO THE EDITOR—Vancomycin way of administration in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections is a controversial issue. In daily practice, many clinicians prefer to use continuous infusion (CoI) instead of intermittent infusion (InI), mainly in severe patients admitted in intensive care units (ICUs). Recently published Infectious Diseases Society of America (IDSA) guidelines for the treatment of MRSA infections do not clarify the issue and state that “because of the lack of a clear benefit over intermittent dosing, and because

time > minimum inhibitory concentration (MIC) is not the primary predictor of efficacy, continuous infusion vancomycin is not recommended" (page e41) [1]. To support this statement, authors refer to 3 studies [2–4]. Because of the high morbidity and mortality associated with severe MRSA infection, we believe that the issue is of paramount importance for clinicians worldwide and respectfully disagree with the evaluation of the cited studies and with the lack of acknowledgment of a large randomized clinical trial comparing CoI with InI of vancomycin [5].

The study by Lacy et al [2] did not investigate CoI of vancomycin, but it compared duration of serum bactericidal activity against MRSA after administration of 2 different intermittent dosages of vancomycin (1 gram every 12 hours vs 1 gram every 24 hours) in healthy volunteers. The vancomycin pharmacodynamic analysis suggested higher activity after a dosage of every 12 hours.

The second study by James et al [3] compared, in a crossover design, the pharmacodynamics and pharmacokinetics of CoI and InI of vancomycin in a small sample size of 10 patients. Although the 2 ways of infusion revealed equivalent pharmacodynamic activities against MRSA and methicillin-susceptible *S. aureus*, CoI was more likely to result in serum bactericidal titers that remained >1:8 for longer duration (100% vs 60% of the dosing intervals) [3].

The last cited study by Wisocki et al [4] compared prospectively 13 patients treated with CoI of vancomycin with 13 matched historical controls treated with InI. No statistically significant difference in terms of clinical outcomes, of time needed to reach therapeutic serum concentration of vancomycin, and of nephrotoxicity rates was found between the 2 groups [4].

Of interest, none of the aforementioned studies investigated the relationship between time greater than MIC and vancomycin efficacy. Although the role of pharmacodynamic parameters

was better explained elsewhere in the guidelines, the sentence "time > MIC is not the primary predictor of efficacy" remains debatable. There is still no definitive evidence of the impact of pharmacokinetic/pharmacodynamic parameters of vancomycin on patient outcome. Vancomycin is a time-dependent antibiotic, and in vitro studies clearly showed lack of concentration-dependent killing and short postantibiotic effect against staphylococci, thus suggesting that time greater than MIC is important for its efficacy [6, 7].

Of surprise, the strength of the recommendation not to use CoI vancomycin, according to the guidelines, is AII. However, the largest randomized clinical trial comparing CoI with InI of vancomycin published to date [5] was not included among the retrieved references. The multicenter, prospective, randomized study compared CoI (targeted plateau drug serum concentrations of 20–25 mg/L) and InI of vancomycin (targeted trough drug serum concentrations of 10–15 mg/L) in 119 critically ill patients. Microbiological and clinical outcomes and safety were similar. Patients receiving CoI reached the targeted concentrations significantly faster and had a significantly lower variability in drug exposure. The 10-day treatment cost per patient was \$454 in the InI group and \$321 in the CoI group (23% lower; $P < .01$) [5].

Of note, more recent studies suggest advantages of a CoI vancomycin regimen, such as minor risk of nephrotoxicity [8, 9], faster and/or more frequent achievement of therapeutic serum concentrations and more sustained concentrations [5, 8, 10], and lower mortality rate [11].

In conclusion, we agree with the authors that the available evidence is not sufficient to provide a definitive recommendation to use CoI, compared with InI, of vancomycin; however, we believe that guidelines should provide readers with all relevant data and suggest

that the research agenda needs to move to multicenter studies applying randomized design in selected and homogenous populations. This would provide better evidence of external validity and the power to measure cost-effectiveness and exclude important adverse clinical outcomes.

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