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Observational clinical study on the effects of different dosing regimens on vancomycin target levels in critically ill patients: Continuous versus intermittent application

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Summary Different dosing regimens for vancomycin are in clinical use: intermittent infusion and continuous administration. The intention of using these different dosing regimens is to reduce toxicity, to achieve target levels faster and to avoid treatment failure. The aim of this phase IV study was to compare safety and effectiveness in both administration regimens. The study was conducted in 2010 and 2011 in three postoperative intensive care units (ICUs) in a tertiary care university hospital in Berlin, Germany. Adult patients with vancomycin therapy and therapeutic drug monitoring were included. Out of 675 patients screened, 125 received vancomycin therapy, 39% with intermittent and 61% with continuous administration. Patients with continuous administration achieved target serum levels significantly

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earlier (median day 3 versus 4, $p = 0.022$) and showed fewer sub-therapeutic serum levels (41% versus 11%, $p < 0.001$). ICU mortality rate, duration of ICU stay and duration of ventilation did not differ between groups. Acute renal failure during the ICU stay occurred in 35% of patients with intermittent infusion versus 26% of patients with continuous application ($p = 0.324$). In conclusion, continuous administration of vancomycin allowed more rapid achievement of targeted drug levels with fewer sub-therapeutic vancomycin levels observed. This might indicate that patients with more severe infections or higher variability in renal function could benefit from this form of administration.

Introduction

The glycopeptide vancomycin was introduced into the anti-infective armamentarium in the 1950s, before modern pharmacodynamic and pharmacokinetic methods were established to guide dosing practices [1,2]. More than 50 years of routine usage and research followed and the agent has been well characterized. Recommendations have changed over time, and higher vancomycin trough serum levels are desired, especially in severe infection, depending on the pathogen identified. Although widely debated, there are recommendations that trough levels of between 15 and 20 mg/L should be achieved to prevent development of resistance and to achieve sufficient serum tissue levels [3]. Nevertheless, it remains a clinical challenge to merge all available patient-based data, e.g., location of infection, weight, glomerular filtration rate, co-morbidities and co-medication, into suitable dosing guidelines and thereby use this information to achieve appropriate trough serum levels [4]. Recently, the frequency of therapeutic drug monitoring (TDM) and appropriate vancomycin utilization were verified in a prospective trial evaluating the clinical and educational value of additional intensive care unit (ICU) chart reviews by clinical pharmacists [5]. In contrast, nomograms have been analyzed with the intention to improve dosing patterns, but they failed to help in achieving sufficient vancomycin serum levels [6]. Similarly, using dosing recommendations provided by the current vancomycin product information has been demonstrated to be even worse for obtaining target serum levels [7]. Consequently, TDM is recommended to guide vancomycin therapy [3], and data from a recent clinical trial showed that repeated measurements increase the safety of target serum levels in a subset of medical ICU patients [8].

Vancomycin interacts with cell wall synthesis in gram-positive bacteria, and there has been controversy regarding the optimal pharmacological description [9]. Some authors have reported time-dependent bacterial killing properties, and others have favored concentration-dependent models for vancomycin. Two dosing regimens are repeatedly discussed with the intention of optimizing vancomycin serum levels and subsequent patient outcome. Intermittent administration regimens may be beneficial with regard to possible post-antibiotic effects described in several experimental settings, without being definitively proven in clinical studies [10—12]. Continuous infusion may achieve target plasma levels faster. This dosing regimen was described to achieve more stability in the area under the serum concentration—time curves (AUC) combined with the possibility to measure serum levels earlier [12—14]. Clinical data comparing both dosing regimens are limited and there remains uncertainty regarding optimal dosing strategies in ICU patients. In this context, this study was performed to evaluate the effectiveness and safety of the two different dosing regimens for vancomycin for empirical anti-infective treatment in surgical ICU patients.

Materials and methods

Study design and setting

This trial represents a phase IV study, including surgical patients treated in three ICUs at Charité university hospital, a tertiary medical care center in Berlin, Germany. The study is based on a secondary analysis of prospectively obtained data from a larger interventional clinical trial on antibiotic stewardship from 2010 and 2011, conducted to improve guideline adherence in critically ill patients [15].

Patients, data collection and measurement

Adult patients were screened for study inclusion by having an ICU stay of at least 36 h. Inclusion criteria