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Implementation of a protocol for administration of vancomycin by continuous infusion: pharmacokinetic, pharmacodynamic and toxicological aspects

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ABSTRACT

Optimising antibiotic administration is critical when dealing with pathogens with reduced susceptibility. Vancomycin activity is dependent on the area under the concentration–time curve over 24 h at steady-state divided by the minimum inhibitory concentration (AUC/MIC), making continuous infusion (CI) or conventional twice daily administration pharmacodynamically equipotent. Because CI facilitates drug administration and serum level monitoring, we have implemented a protocol for CI of vancomycin by: (i) examining whether maintaining stable serum concentrations (set at 25–30 mg/L based on local susceptibility data of Gram-positive target organisms) can be achieved in patients suffering from difficult-to-treat infections; (ii) assessing toxicity ($n = 94$) and overall efficacy ($n = 59$); and (iii) examining the correlation between AUC/MIC and the clinical outcome in patients for whom vancomycin was the only active agent against a single causative pathogen ($n = 20$). Stable serum levels at the expected target were obtained at the population level (loading dose 20 mg/kg; infusion of 2.57 g/24 h adjusted for creatinine clearance) for up to 44 days, but large intrapatient variations required frequent dose re-adjustments (increase in 57% and decrease in 16% of the total population). Recursive partitioning analysis of AUC/MIC ratios versus success or failure suggested threshold values of 667 (total serum level) and 451 (free serum level), corresponding to organisms with a MIC > 1 mg/L. Nephrotoxicity potentially related to vancomycin was observed in 10% of patients, but treatment had to be discontinued in only two of them.

1. Introduction

The pharmacokinetic/pharmacodynamic index governing the antibacterial activity of vancomycin is the area under the concentration–time curve over 24 h at steady-state divided by the minimum inhibitory concentration [1] (AUC/MIC; see [2] for definition), with a value of at least 400 for optimal activity [3]. Thus, vancomycin could be administered by discontinuous infusion as well as by continuous infusion (CI) as far as efficacy is concerned. North American guidelines recommend administering vancomycin as a twice daily or three times daily schedule (doses given in ca. 1 h every 12 h or 8 h apart) and to monitor trough levels [4]. This, however, does not allow accurate determination of the AUC since peak levels, primarily influenced by the volume of distribution (V_d), remain undetermined. In contrast, CI may provide an immediate reading of the AUC value. Actually, CI of vancomycin was shown to allow for a better attainment of target concentrations [5] and to ensure at least equal efficacy, whilst affording equal or decreased toxicity (see [6] for a recent meta-analysis). CI also greatly facilitates the monitoring of vancomycin (since serum levels should not be affected by the time of sampling) and has practical advantages for nursing [5,7,8]. It also allows for a centralised preparation of ready-to-use infusion sets, adapted for administration through volumetric devices, further minimising the risks of dose and timing errors [9]. We report here on the hospital-wide implementation of vancomycin administration for non-intensive care unit (non-ICU) patients under the supervision of a clinical pharmacist and an infectious diseases physician, and we present an analysis of the pharmacokinetics (including the determination of free versus total

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serum levels), the clinical outcomes and the correlations between AUC/MIC and clinical success.

2. Materials and methods

2.1. Overall design, setting, patients and ethical considerations

The investigation was performed over a 13-month period in the non-ICU wards (see caption of Fig. 1) of a 420-bed teaching hospital. Eligible patients were those for whom vancomycin treatment was prescribed for suspected or documented infection according to local guidelines. Excluded patients were those with life expectancy <1 week, baseline serum creatinine >2.3 mg/L or a creatinine clearance <30 mL/min at initiation of treatment, or those who already received vancomycin within 48 h prior to the current infection. All enrolled patients were examined for quality of administration, overall clinical efficacy and side effects, and benefited from dose adaptation based on availability of serum levels (usually once a week). A subset of patients who provided specific informed consent was included for detailed pharmacokinetic analysis with daily follow-up of serum levels and subsequent/eventual dose adaptation. The protocol of the study was approved prior to initiation by the Ethical Committee of the CHU Mont-Godinne (Yvoir, Belgium) and written informed consent was obtained from all patients (or a close relative if the patient was unable to co-operate) for investigations beyond the local standard of care.

2.2. Treatment

Vancomycin (Vancocin®; Lilly, Illkirch, France) 10 g/L in 5% glucose solution for infusion was prepared in the Central Pharmacy and was administered by volumetric infusion pump (Volumed® 7000; Arcomed AG, Regensdorf, Switzerland). Patients received a loading dose of 20 mg/kg (based on actual body weight and an estimated V_d of 0.7 L/kg [10–12]) administered over 1 h for doses <2 g or over 2 h for larger doses. This was immediately followed by CI at a rate K_o (mg/min) calculated according to Eq. (1):

$$K_o = C_{ss} \times 0.65 \times \text{CCrCl} \quad (1)$$

where C_{ss} (mg/L) is the total serum target concentration at steady state, CCrCl is the calculated creatinine clearance (in L/min, based on the Cockroft–Gault formula [13] using total body weight) and 0.65 is a correction factor for prediction of vancomycin clearance from CCrCl [12,14]. Because of the limitations of the Cockroft–Gault formula, CCrCl values >120 mL/min were ignored (38/94 patients) and those patients were dosed as if having a creatinine clearance of 120 mL/min. Our initial serum concentration target value was 27.5 mg/L, corresponding to a daily dose of 2.57 g for an ideal patient (CCrCl = 0.1 L/min; male), and, based on the preparation made, an infusion at 10.7 mL/h (rounded to 11 mL/h for practical purposes). For patients not enrolled in the detailed pharmacokinetic analysis (described in Section 2.5), a first sample was obtained within 8–12 h after initiation of CI and dosing was re-adjusted by increasing or decreasing the speed of the volumetric device by 500 mg increments. A new loading dose was administered if the total vancomycin serum concentration was <15 mg/L. Sampling and dose adjustments were repeated daily using pre-defined criteria (see Supplementary Table SP1) until two consecutive levels in the target range (25–30 mg/L) were obtained, after which samples were taken at least once weekly. Additional details regarding the stability of vancomycin and its compatibility with other antibiotics and other drugs have been published recently [15].

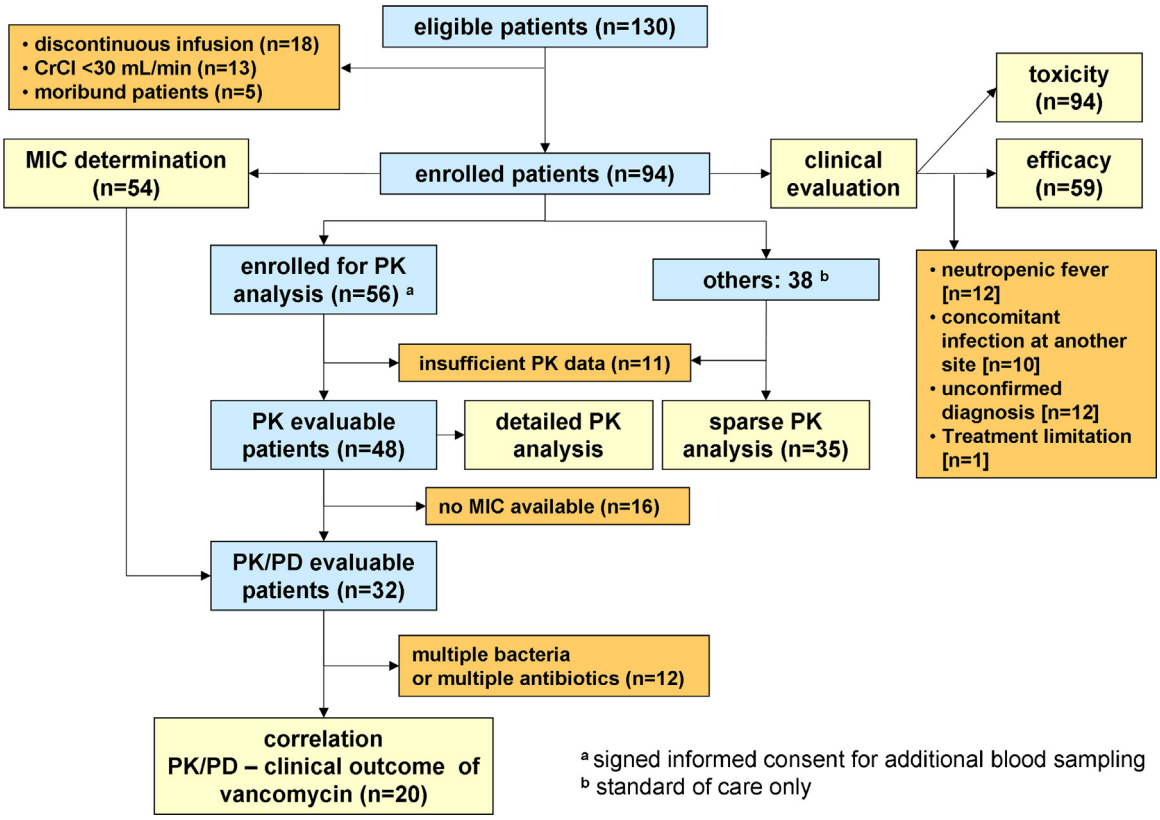

Fig. 1. General outline of the study and number of patients in each group or subgroup. Patients were from the following wards: cardiology (n = 4); cardiovascular surgery (n = 7); general surgery (n = 7); gastroenterology (n = 3); geriatrics (n = 7); haematology (n = 31); internal medicine (n = 8); neurosurgery (n = 2); oncology (n = 6); orthopaedic surgery (n = 10); pneumology (n = 6); and urology (n = 3). CrCl, creatinine clearance; MIC, minimum inhibitory concentration; PK, pharmacokinetics; PD, pharmacodynamics.