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Continuous Infusion of Vancomycin in Methicillin-Resistant Staphylococcus Infection

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Key Words
Vancomycin
Methicillin-resistant staphylococcus infection
Continuous infusion

Abstract

Objective: The aim of the study was to verify the therapeutic response of vancomycin in methicillin-resistant staphylococcus infection (MRSA/MRCNS) administered according to two different methods (intermittent infusion vs. continuous infusion). **Method:** Experimental plan: retrospective study; study environment: university hospital, two intensive care units. Twenty-five critically ill patients submitted to antibiotic treatment with vancomycin for infection from MRSA/MRCNS were studied. The patients, who were classified according to SAPS II scores, were divided into two groups: group A (n = 14): dose of vancomycin of 0.5 g × 4/day and group B (n = 11): dose of 2 g/day of vancomycin administered in a continuous infusion. Before the antibiotic therapy was started (T1) and prior to its end (T2), the following parameters were evaluated: degree of impairment of the main organs and systems by means of sepsis-related organ failure assessment score (SOFA) and count of the white blood cells (WBC). The length of the hospital stay during intensive care was calculated for both groups (statistics: Student t test). **Results:** No significant differences were found in the SAPS II scores and in the length of the hospital stay. In a comparison of the T1 and T2 results, we noted that patients of group A had no variations in the SOFA scores (4.84 ± 2.48 vs. 4 ± 3.9) and in the WBC mean values (12,415 ± 5,099 vs. 12,841 ± 6,864 cells/mm^3). In contrast, in the patients of group B, we noted significant variations ($p < 0.05$) in the mean values of the SOFA scores (6.62 ± 2.2 vs. 4.37 ± 3.5) and in the mean values relative to the WBC count (17,242 ± 12,842 vs. 10,757 ± 3,610 cells/mm^3). **Conclusions:** In critically ill patients suffering from MRSA/MRCNS infection, vancomycin administration in continuous infusions improved organ function and leukocyte response, but did not seem to modify the overall evolution of the disease.

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Introduction

Vancomycin, a glycopeptide antibiotic utilized in the treatment of methicillin-resistant staphylococcal (MRSA/MRCNS) infections, belongs to those antibiotics (like the β-lactams) whose efficacy is 'time-dependent' [1, 2]. For this reason, it has been hypothesized that its administration in a continuous infusion would be more efficacious than in an intermittent infusion [3]. In fact, after the minimum inhibitory concentration (MIC) has been reached, the continuous-infusion technique makes it possible to obtain a constant plasmatic concentration, the opposite of the intermittent-infusion technique which produces 'discontinuous' concentrations with peaks that are too high (potentially toxic) and insufficient trough levels [3].

Starting from these considerations, we performed the following retrospective study in order to verify whether two different methods of administering vancomycin (i.e. intermittent vs. continuous) have a different therapeutic efficacy in the treatment of MRSA/MRCNS infections in critically ill patients.

Materials and Methods

The clinical study was performed with a population of critically ill patients (n = 25) having recovered in intensive care over a period of 7 months. They received an antibiotic therapy with vancomycin for a documented MRSA/MRCNS infection (positive culture on a biological sample) and for a period longer than 5 days, until the infective episode was cured (negative culture on the same type of biological sample). More information on MRSA/MRCNS infection is given in table 1.

Table 1. Strains and clinical sample of methicillin-resistant staphylococcus infection

	Group A (n = 14)	Group B (n = 11)
MRSA/MRCNS	8/6	6/5
Bronchial sputum	8	5
BAL	2	3
Blood culture	4	3

After their informed consent had been obtained, the patients, who were classified with the SAPS II severity of illness score [4], were divided into two groups on the basis of two different treatment schedules. The 14 patients belonging to group A were treated with 0.5 g × 4 (every 6 h/day of vancomycin, while the other 11 patients of group B were treated with a continuous infusion of vancomycin at a rate of 83 mg/h. The latter infusion was preceded by a bolus dose of 500 mg, administered over 10 min in order to attain the effective plasma concentration of the drug in a short time. Vancomycin therapy continued for almost 5 days and/or until the end of infection symptoms or signs. During treatment with vancomycin, all patients received an antibiotic coverage against gram-negative rods with monobactams or aminoglycosides. The pathophysiological characteristics of the patients belonging to the two groups are reported in table 2. The exclusion criteria were the following: age <18 years, pregnancy, severe renal failure (creatinemia higher than 5 mg/dl), AIDS, and history of hypersensitivity to glycopeptides. In all patients, vancomycin plasma concentrations after 2 h and every 48 h after the first administration were determined with the HPLC method. The following parameters were evaluated both at the beginning (T1) and at the end ot the therapy (T2): degree of impairment of the main organs and systems by means of a scoring system (table 3) called the sepsis-related organ failure assessment score [5], WBC count (hemochromocytometric examination) and fever. The mean length of hospitalization in intensive care during intensive care was calculated in all patients. All values were expressed as means (± SD). The statistical analysis was made by comparing the means at the two different evaluation times (T1 and T2) with the Student t test. Values of $p < 0.05$ were considered statistically significant.

Results

No significant differences concerning age, weight, SAPS II scores and the mean length of hospitalization (table 2) were observed be-

Table 2. Pathophysiological characteristics of patients (n = 25) considered in the study

	Group A (n = 14)	Group B (n = 11)	p (t Student)
Sex, m/f	11/3	9/2	
Age, years	63 ± 24	70 ± 14	NS
Weight, kg	65 ± 11	61 ± 10	NS
SAPS II, score	44 ± 13	50 ± 9	NS
Hospitalization, days	15 ± 3	13 ± 4	NS
Pathologies			
Cardiogenic shock	4	3	
Multitrauma	3	1	
Head trauma	2	2	
New acute COAD	2	1	
Pulmonary embolism	2	1	
Previous AMI in postoperative patients	1	2	
Polyneuropathy		1	

COAD = Chronic obstructive airway disease, AMI = acute myocardial infection.

tween the two patient groups. Plasma vancomycin concentrations over the first 5 days are summarized in table 3. Vancomycin therapy continued for 6.09 ± 1.34 days in group A and for 6.14 ± 1.37 days in group B. A resolution of the fever, tachycardia and tachypnea was obtained in both groups. Group A showed no significant differences in the SOFA scores and WBC number reported before vancomycin treatment and after the end of treatment. Group B, on the other hand, showed a significant reduction ($p < 0.05$) of the SOFA scores (T1 = 6.6 ± 2.2; T2 = 4.37 ± 3.5) and a significant difference ($p < 0.05$) between the WBC number at T1 (17,242 ± 12,842 cells/mm^3 and at T2 (10,757 ± 3,610 cells/mm^3; table 4). There were no significant intervariabilities between the mean values found at T1 in the two groups (table 4).

Four patients had mixed infections (n = 4; group A:B = 2:2; strain: *Klebsiella pneumoniae* n = 2, Pseudomonas n = 2) and they were treated with vancomycin plus aminoglycoside or monobactam antibiotics. The other patients were treated with aminoglycosides or monobactams to prevent the spontaneous growth of gram-negative strains. There were no adverse effects in the two groups to vanco-

Table 3. Serum vancomycin concentrations (mean ± SD, μg/ml) in 25 critical patients with two different vancomycin schedule administrations

	GA (n = 14)	GB (n = 11)
D1	15 ± 3.5	13.88 ± 5.7
D2	22.5 ± 5.6	17.76 ± 7.6
D3	30.7 ± 6.4	24.3 ± 3.9

For intermittent administrations peak concentration was evaluated (30 min after bolus). GA = Intermittent infusion of 0.5 g × 4; GB = continuous infusion of 83 mg/h after initial bolus of 0.5 g. The determinations were performed at these times: D1 = 2 h after bolus administration; D2 = 48 h after the start of the therapy; D3 = 96 h after the start of the therapy.

Table 4. Mean variations in the SOFA score and in the WBC count reported in the two groups of patients treated with vancomycin (see Methods)

	T1	T2	p (T1 vs. T2)
SOFA score			
Group A	4.83 ± 2.48	4 (± 3.9)	NS
Group B	6.62 ± 2.2	4.37 (± 3.5)	<0.05
p (A vs. B)	NS		
WBC, cells/mm^3			
Group A	12,415 (± 5.099)	12,841 (± 6,864)	NS
Group B	17,242 (± 12,842)	10,757 (± 3,610)	<0.05
p (A vs. B)	NS		

mycin administration and the red man neck syndrome had never occurred in the two groups.

Discussion and Conclusions

The therapeutic efficacy of an antibiotic depends on different variables (the susceptibility of the causative organism, the site of the infection) and on the pharmacodynamic and pharmacokinetic properties (intrinsic antimicrobial activity, elimination half-life, time-concentration profile, protein binding) [6]. In critically ill patients, antibiotic therapy is further influenced by concomitant factors (hemodynamic alterations, increased capillary permeability, renal function impairment) which may interfere with its pharmacological characteristics, above all as far as the tissue distribution and the maintenance of adequate plasmatic concentrations are concerned [6]. Vancomycin is an antibiotic with a 'time-dependent' efficacy with a slow bactericidal activity which is maximal on bacteria in the exponential growth phase [2]. In healthy volunteers, the pharmacokinetics of vancomycin is described according to a 3-compartment model with a half-life of 4–8 h with considerable individual variations. In order to obtain a therapeutic effect on serious staphylococcal infections, the maintenance of a peak level ranging from 30 to 40 mg/l seems necessary with trough concentrations at least higher than 5 or equal to 10 mg/l [7].

As already mentioned, in critical conditions it is not always possible to maintain these therapeutic levels, and the dosage of vancomycin may vary considerably [1]. Another parameter that can modify the therapeutic efficacy of vancomycin administered as intermittent doses is the so-called postantibiotic effect which for *Staphylococcus aureus* is in the order of 2–4 h [1]. Beyond this period, bacterial growth resumes and with it, the phlogistic response of the organism. These considerations have resulted in some authors to utilizing this antibiotic with a continuous infusion. In 1993, Brinquin et al. [8] used the continuous infusion of vancomycin in doses of 50 mg/kg/day in the treatment of postoperative meningitis in patients undergoing to neurosurgical operations of varying severity. This treatment schedule was maintained for a minimum of 3 up to a maximum of 6 weeks with a resolution of the infection in all cases and without any particular side effects (i.e. nephrootoxicity). Subsequently, Conil et al. [9] utilized a similar treatment in seriously burnt patients whom after the intermittent administration of vancomycin in a dosage of 30 mg/kg had a rapid hale in plasma concen-

trations. These authors had studied 18 seriously burnt patients (with a burn surface area of about 40%) and who were suffering from a MRSA/MRCNS infection. These patients were treated with a continuous infusion for an average period of 17 days, with the dosage maintained at 30 mg/kg over 24 h; the resolution of this infection was obtained without toxic side effects (even if it was demonstrated that in 80% of the patients, the dosage was inadequate since the observed plasma levels were insufficient and less than 15 mg/l).

In our study, we studied a population of critically ill patients with various pathologies; we divided them retrospectively into two groups on the basis of the modality according to which the vancomycin was administered.

The severity of disease in all the patients was classified with the SAPS II system [4] which, as is well known, takes into account age, several hemodynamic physiological variables, body temperature, daily urinary output, several hematochemical examinations and several indexes such as the PaO_2/FiO_2 ratio for respiratory functionality and the Glasgow Coma Scale for an evaluation of the impairment of the cerebral functions. The other parameters considered take into account the possible presence of concomitant pathologies with an unfavorable prognosis (AIDS, metastatic cancer, malignant hematological diseases) and the area of origin (medical, surgical) associated with the degree of emergency. We then studied three parameters of clinical evaluation which would make it possible to check the response to the two types of treatment: the WBC response and the SOFA scores (table 4). The latter has recently been suggested for the purpose of classifying the degree of dysfunction of the various organs and systems in septic patients; it appears to be useful in verifying the treatment efficacy [5].

The SOFA score is more efficacious than the SAPS II to evaluate the evolution of the course of the illness, in fact SAPS II is applicable (statistically correct use) only in the first 24 h after admission; in contrast the SOFA score is applicable every day during the stay in the intensive care unit.

Therefore, while the SAPS II score is useful to compare the severity of the disease and the probability of death, the SOFA score is useful to evaluate the consequences of the pathology during the course of disease.

The patients entered in this study were given intensive care over a determined period of time for at least 5 days. They had a SAPS II score of between 31 and 59 points with considerable organ impairment, while the SOFA scores demonstrated the dysfunction of at least two systems; the differences in the SOFA score at the beginning of infection were not statistically significant, showing no differences in the severity of illness.

If we compare the values of the two groups, it can be seen that in group A the SOFA score and the mean WBC value are lower than those of group B. This difference, which is not significant, may be partly linked to the type of intensive treatment received by these patients, which may be influenced by different variables that should not be overlooked (type of ventilatory support, fluids therapy). In addition, while these values remain almost unmodified in the first group, there is a significant reduction of the SOFA score and leukocytosis in the second group.

The inflammatory response seems to evolve more favorably in those patients receiving vancomycin in a continuous infusion. This could depend on the greater antimicrobial efficacy of this treatment, but also on the possible limiting of the inflammatory response. In fact, from a pathophysiological point of view, the infection is definitely one of the stimuli capable of triggering off in immunocompetent patients the phlogistic response of the organism which, as is well known,

determines a series of alterations in the microcircle that are at the basis of organ dysfunction [10].

These are known as 'cascade' mechanisms: they continue for a long time, sustained by vicious circles of reciprocal activation and are for the most part able to sustain themselves (complement, macrophages, cytokines, coagulation) [10].

During the course of therapy with a β-lactam or a glycopeptide 'time-dependent' antibiotic like vancomycin, it is possible that discontinuous administration can facilitate bacterial growth during the dose intervals (which, obviously, are characterized by a low plasmatic drug concentration), permitting the causative organism to nourish the phlogistic response and the activation of the above-described systems. Continuous infusion might avoid this problem, since it would make it possible to maintain plasmatic concentrations at values that are 3 or 4 times higher than the MIC.

In conclusion, on the basis of the results obtained in this study and of what has already been discussed in the literature, it appears possible to affirm that (1) the continuous infusion of vancomycin into a critically ill patient who has an MRSA/MRCNS infection can determine an improvement in the leukocytic response, and (2) this improvement has a positive reflex on organ function, but does not seem capable of having an effect on the evolution of the disease. In any case, it is necessary to take into account the limits of this study, which has the characteristics of a retrospective analysis. Before arriving at any definitive conclusions, a prospective clinical study would be useful, which could confirm the initial hypothesis and sustain the results that we have presented and discussed here.

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