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Pharmacokinetic–pharmacodynamic aspects of antimicrobial prophylaxis with teicoplanin in patients undergoing major vascular surgery

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Abstract

A prospective, two-arm, open study assessing plasma exposure to teicoplanin with two different prophylactic regimens (Group A ($n = 23$), 800 mg pre-operatively versus Group B ($n = 24$), 400 mg pre-operatively plus two doses of 200 mg 24 h apart) was carried out in patients undergoing major vascular surgery. The intent was to define the feasibility and the possible advantages of the single pre-operative high dose in ensuring therapeutically effective plasma concentrations (>10 mg/L) of teicoplanin even during long-lasting operations. At the end of the intervention, mean teicoplanin concentrations (±S.D.) were 14.05 ± 5.13 mg/L and 5.39 ± 2.13 mg/L in Groups A and B, respectively. At 24 h, average teicoplanin levels were 5.10 ± 1.25 mg/L and 2.08 ± 0.73 mg/L in Groups A and B, respectively; at 48 h they declined to 2.86 ± 0.70 mg/L in Group A, whereas they rose to 2.67 ± 0.82 mg/L after administration of 2.63 ± 0.51 mg/kg at 24 h in Group B. Single pre-operative high-dose teicoplanin may ensure effective plasma levels even in cases of very long-lasting operations (>8 h) with no need for intraoperative re-dosing and may enable more appropriate prophylactic exposure than that achievable with the same total dose given in three administrations 24 h apart.

Keywords: Teicoplanin; Surgical prophylaxis; Pharmacodynamics/pharmacokinetics; Therapeutic drug monitoring

1. Introduction

Interventions of major vascular surgery are considered clean operations [1], which may be complicated by a moderate incidence of surgical site infections (SSIs). Although infrequent, SSIs may have devastating consequences during vascular surgery when involving the prosthetic graft [2,3].

Antibiotic prophylaxis in vascular surgery has been proven beneficial to reduce SSIs after reconstruction of the aorta, procedures on the leg that involve a groin incision, any procedure that implants a vascular prosthesis or endoluminal stent, and lower extremity amputation for ischaemia [4]. Since the major goal of antimicrobial prophylaxis is to counteract the most frequently contaminating pathogens at the surgical site

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during the operation time, the appropriate antibiotic in terms of microbial coverage and the timing of administration should be chosen [5].

Considering that Gram-positive microorganisms deriving from the patient's skin and/or from the operators, namely *Staphylococcus epidermidis* and *Staphylococcus aureus*, are the most frequently involved pathogens, cefazolin or cefamandole are frequently considered the antibiotics of choice [6]. Conversely, in settings with a high prevalence of methicillin resistance, glycopeptides are often the preferred prophylactic agents [7,8], although no definitive guidelines stating when to use this alternative choice have been developed [6,9,10]. Glycopeptides should be used wisely with the intent of avoiding the spread of resistance [11], although the prophylactic role of teicoplanin in cardiovascular surgery has been supported by some authors [12,13]. Additionally, although not always proven to be more effective than β-lactams for prevention of SSIs [14–16], glycopeptides were postulated to be particularly advantageous during cardiovascular procedures involving implants, considering the possible negative impact of SSIs occurring in this context [17].

However, the use of a standard 400 mg teicoplanin loading dose for prophylaxis during vascular surgery could cause underexposure, consistent with the need for high loading doses for early achievement of therapeutically relevant concentrations either in prophylaxis during cardiac surgery [18,19] or in the treatment of critically ill patients [20].

Additionally, a frequent incongruous practice in the handling of antimicrobial prophylaxis during cardiovascular surgery, especially in the past but still persisting today, is the post-operative administration of antibiotics for 2–3 days. Although ultrashort or short regimens should be preferred in cardiovascular surgery [15,21], some authors still continue supporting the opportunity for longer regimens [22,23].

On these bases, a prospective, two-arm, open study assessing teicoplanin plasma exposure achievable with two different prophylactic regimens using the same total drug amount (800 mg) was carried out in patients undergoing major vascular surgery. The intent of this study was to define the feasibility and the possible advantages of a single pre-operative high dose in ensuring therapeutically effective plasma concentrations (>10 mg/L) even during long-lasting operations and, conversely, to highlight the inconsistency of longer low-dose prophylactic regimens in this setting.

2. Patients and methods

Forty-seven consecutive patients undergoing major vascular surgery at the 3rd Division of General Surgery of the Spedali Civili of Brescia were randomly assigned to one of the two study groups: Group A ($n = 23$) was administered 800 mg of teicoplanin pre-operatively; and Group B ($n = 24$) was administered 400 mg pre-operatively and two further doses of 200 mg each 24 h apart. The pre-operative dose of teicoplanin was administered as a 5 min intravenous bolus at the time of induction of anaesthesia, ca. 30 min before starting the operation. The study was approved by an internal review board and informed consent for blood sampling was obtained from each subject. This comparative study was carried out with the intent of demonstrating that, using the same total amount of administered drug per patient (800 mg), the Group A strategy may provide more appropriate exposure than the Group B strategy, which, owing to its longer duration, would appear to be more appealing to surgeons. Considering that teicoplanin exhibits a time-dependent antibacterial activity, the time during which the plasma concentration persists above the minimum inhibitory concentration (MIC) against the pathogens during the interventional period ($T > \text{MIC}$) must be considered the most important pharmacodynamic determinant of efficacy. Although $T > \text{MIC}$ must be at least 50% of the dosing interval to ensure standard efficacy with these agents [24,25], the target pharmacokinetic goal during antimicrobial prophylaxis in elective surgery should be to maintain the plasma concentration of free antibiotic higher than the MIC of the potentially contaminating pathogens for the entire intervention (minimum plasma concentration (C_{min}) > MIC) [5,26].

Blood samples to determine teicoplanin plasma concentrations were collected at the time of wound closure, at 24 h and at 48 h after administering the pre-operative dose. After centrifugation, plasma samples were stored frozen at −80 °C and subsequently analysed at the Institute of Clinical Pharmacology and Toxicology of the University of Udine by means of a fluorescence polarisation immunoassay (Opus Diagnostics, Fort Lee, NJ) using a TDx analyser (TDx, Abbott, Rome, Italy) [27,28]. The interday and intraday coefficients of variation of the assay were less than 10%.

Optimal exposure for antimicrobial prophylaxis with teicoplanin was defined as a plasma level persisting above 10 mg/L at the time of wound closure, as this value is considered the standard threshold for efficacy with teicoplanin [29,30]. Since patients received standard dosages, to avoid bias due to interindividual differences in body weight the teicoplanin levels at time of wound closure were normalised with respect to teicoplanin dose per kg.

3. Results

Patient characteristics are listed in Table 1. No statistically significant differences between the two study groups were documented. Scatter plots of teicoplanin plasma levels at the time of wound closure and at 24 h and 48 h after the first pre-operative dose are depicted in Figs 1 and 2, respectively. At the end of the intervention, mean teicoplanin concentrations (±S.D.) were 14.05 ± 5.13 mg/L in Group A after a mean pre-operative dose of 11.10 ± 1.66 mg/kg,