Research

Pruritus: a useful sign for predicting the haemodynamic changes that occur following administration of vancomycin

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Introduction
Vancomycin is among the most effective antibiotics for treatment of methicillin-resistant Staphylococcus aureus infections [1–4], and it is widely used prophylactically in cardiac surgery [5–7]. Among the adverse effects of vancomycin (apart from nephrotoxicity and ototoxicity), anaphylactoid reactions may occur, which manifest clinically as cutaneous rash, pruritus (‘red man’ syndrome), hypotension and broncospasm [4,8,9]. These reactions are caused by histamine release, and are not mediated by an immunological mechanism [10,11].

In our cardiosurgical center vancomycin is administered prophylactically before induction of anaesthesia in all patients undergoing open-heart surgery, and in some such patients we

CI = cardiac index; PaO₂ = arterial oxygen tension; PVRI = pulmonary vascular resistance index; Qsp/Qt = shunt fraction; SVI = stroke volume index; SVRI = systemic vascular resistance index.

Abstract

Introduction The aim of this study was to investigate the haemodynamic changes that follow the appearance of pruritus during vancomycin administration.

Methods We studied 50 patients scheduled for coronary artery bypass surgery, and we compared data from patients who exhibited pruritus with those from patients who did not. After the monitoring devices had been positioned, vancomycin (15 mg/kg) was continuously infused at a constant rate over 30 min, before induction of anaesthesia. Haemodynamic profiles were recorded before vancomycin infusion (time point 1); at 15 (time point 2) and 30 min (time point 3) after the beginning of vancomycin infusion; and 15 min after vancomycin infusion had been stopped (time point 4). At each time arterial and mixed venous blood samples were drawn to calculate the shunt fraction (Qsp/Qt).

Results In patients who exhibited pruritus (group A, n = 17) at time point 3 versus time point 1, systemic vascular resistance index (SVRI) and arterial oxygen tension (PaO₂) decreased significantly; cardiac index (CI), stroke volume index (SVI) and Qsp/Qt increased significantly; and mean systemic pressure and heart rate were stable. Those changes were observed only in patients not treated with a β-blocker before surgery, whereas no change occurred in patients treated with the drug. In the patients who were free from pruritus (group B, n = 28), we did not observe any significant change.

Conclusion The appearance of pruritus during vancomycin administration indicates that SVRI is declining, thus exposing the patient to risk for hypotension. Therapy with a β-blocker appears to confer protection against this hemodynamic reaction.

Keywords haemodynamics, shunt fraction, pruritus, respiratory gases exchange, vancomycin
have observed the occurrence of pruritus, localized or generalized, during infusion of the antibiotic. We therefore conducted the present study to investigate the haemodynamic behaviour that follows the occurrence of pruritus, and to compare it with that observed in patients who are free from this clinical sign.

**Patients and methods**

We studied 50 patients undergoing elective coronary artery bypass surgery, following approval from the local ethics committee and once written informed consent had been obtained from each patient. Admission criteria to the study were as follows: stable preoperative haemodynamic conditions, no intravenous cardiovascular therapy, no preoperative diuretic therapy, sinus rhythm, no history of anaphylactic reactions, and normal hepatic and renal function.

Preoperative therapy was continued until the morning of the operation. Premedication consisted of morphine (0.1 mg/kg) and scopolamine (0.005 mg/kg), administered intramuscularly 1 hour before the patient entered the operating room. After the monitoring devices had been positioned (electrocardiograph leads DII–V5 for ST-segment analysis; radial artery cannula and pulmonary artery catheter [Arrow AH 050050-H, 7.5 F; Arrow International, Inc., Reading, PA, USA] transcutaneous oxygen saturation probe), vancomycin (15 mg/kg) was administered at a constant rate by a syringe pump (DPS Fresenius; Grenoble, France) over 30 min.

A complete haemodynamic profile was taken for each patient at the following time points: before the administration of vancomycin (time point 1); at 15 (time point 2) and 30 min (time point 3) after the beginning of vancomycin infusion; and 15 min after vancomycin infusion had been stopped (time point 4). Apart from collection of haemodynamic data, at each time point two blood samples were drawn (one from the radial artery cannula and another from the distal port of the pulmonary artery catheter) in order to measure arterial and mixed venous blood parameters that are necessary for calculation of Qsp/Qt (i.e. haemoglobin concentration, and oxygen tension and saturation).

Each haemodynamic profile consisted of parameters measured directly (i.e. heart rate, systemic and pulmonary pressures, pulmonary capillary wedge pressure, central venous pressure and cardiac output) and those that were calculated (i.e. SVRI, pulmonary vascular resistance index [PVRI], CI and SVI).

The pulmonary shunt fraction (Qsp/Qt) was calculated using the following equation [12]:

\[
Qsp/Qt = \frac{CcO_2 - CaO_2}{CcO_2 - CvO_2}
\]

Where \( CcO_2 \) is the pulmonary capillary oxygen content, \( CaO_2 \) is the arterial oxygen content, and \( CvO_2 \) is the mixed venous oxygen content.

Analysis of the blood samples was performed by the same operator, using a blood gas system (model 288; Ciba Corning, Medfield, MA, USA) located just outside the operating room.

During the study all patients breathed room air, and crystalloid was continuously infused at a rate of 2 ml/kg per hour, which was increased if necessary to offset a moderate reduction in systemic arterial pressure. If mean blood pressure decreased by more than 20%, then more fluids and/or boluses of ephedrine were infused, vancomycin infusion was temporarily discontinued and the patient was excluded from the study.

The patients were divided into two groups: group A, including patients who exhibited pruritus during vancomycin infusion; and group B, including those patients who did not exhibit pruritus. Each group was then divided into two subgroups on the basis of preoperative therapy with a \( \beta \)-blocker; subgroups A1 and B1 were treated with a \( \beta \)-blocker, whereas subgroups A2 and B2 were not.

The results are expressed as mean ± standard deviation. Data were analysed using Student’s t-test and analysis of variance with Bonferroni correction. \( P < 0.05 \) was considered statistically significant.

**Results**

Group A included 17 patients (subgroup A1, \( n = 11 \); and subgroup A2, \( n = 6 \)) and group B included 28 patients (subgroup B1, \( n = 17 \); and subgroup B2, \( n = 11 \)). Five patients were excluded from the study because of reduction in mean blood pressure by more than 20% (\( n = 2 \)), angina (\( n = 1 \), treated with the intravenous administration of nitroglycerin) and intolerable pruritus (\( n = 2 \)).

Data on the general characteristics of the patients are provided in Table 1. There were no significant differences between the

| Parameter | Group A | Group B |
|-----------|---------|---------|
| Age (years) | 63 ± 7 | 64 ± 8 |
| Weight (kg) | 77 ± 9 | 77 ± 12 |
| LVEF (%) | 55 ± 12 | 50 ± 13 |

Preoperative therapy (\( n \))

| Therapy | Group A | Group B |
|---------|---------|---------|
| \( \beta \)-blocker | 11 | 17 |
| Trinitroglycerin | 18 | 26 |
| Calcium channel blocker | 4 | 7 |
| Digoxin | 0 | 2 |
| ACE inhibitors | 4 | 10 |

No significant difference was observed between the groups in terms of age, weight, left ventricular ejection fraction (LVEF), or preoperative therapy. ACE, angiotensin-converting enzyme.
groups in terms of age, weight, preoperative left ventricular ejection fraction, preoperative therapy, or basal haemodynamic and respiratory data (time point 1, Table 1). Table 2 lists the mean amounts of fluids infused during the study.

At time point 3 as compared with time point 1, patients in group A exhibited a significant reduction (\(P < 0.05\)) in SVRI and PVRI, and a significant increase (\(P < 0.05\)) in CI and SVI (Table 3). Heart rate and mean systemic arterial pressure exhibited a slight but not significant decrease, whereas the other haemodynamic parameters remained stable. At time

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**Table 2**

Mean amounts of fluids infused during the study

| Groups and subgroups | Intravenous fluids (ml) |
|----------------------|-------------------------|
| Group A              | 330 ± 133               |
| Subgroup A1          | 280 ± 67                |
| Subgroup A2          | 421 ± 180               |
| Group B              | 226 ± 40                |
| Subgroup B1          | 230 ± 43                |
| Subgroup B2          | 220 ± 38                |

See text for definitions of groups and subgroups.

**Table 3**

Haemodynamic and respiratory gas modifications at the four time points of the study: whole study population

| Parameter                  | Group | 1      | 2      | 3      | 4      |
|----------------------------|-------|--------|--------|--------|--------|
| HR (beats/min)             | A     | 60 ± 11| 59 ± 11| 60 ± 9 | 58 ± 8 |
|                           | B     | 65 ± 11| 63 ± 12| 64 ± 12| 62 ± 11|
| MSP (mmHg)                 | A     | 85 ± 17| 81 ± 21| 81 ± 18| 84 ± 17|
|                           | B     | 88 ± 18| 88 ± 20| 88 ± 21| 92 ± 20|
| SVRI (dynes·s/cm\(^5\) per m\(^2\)) | A     | 2808 ± 577| 2533 ± 507| 2351 ± 602*| 2559 ± 539|
|                           | B     | 2610 ± 942| 2720 ± 1057| 2544 ± 879| 2821 ± 780|
| CI (l/min per m\(^2\))     | A     | 2.34 ± 0.5| 2.42 ± 0.5| 2.64 ± 0.5*| 2.5 ± 0.4|
|                           | B     | 2.67 ± 0.6| 2.56 ± 0.5| 2.74 ± 0.6| 2.58 ± 0.5|
| SVI (ml/beat per m\(^2\)) | A     | 39 ± 8 | 41 ± 8 | 44 ± 7* | 43 ± 9 |
|                           | B     | 42 ± 11| 41 ± 9 | 43 ± 10| 42 ± 10|
| MPP (mmHg)                | A     | 15 ± 4 | 15 ± 5 | 15 ± 4 | 16 ± 5 |
|                           | B     | 15 ± 4 | 16 ± 5 | 15 ± 6 | 16 ± 7 |
| PCWP (mmHg)               | A     | 8 ± 3  | 9 ± 4  | 8 ± 3  | 8 ± 4  |
|                           | B     | 7 ± 3  | 7 ± 3  | 6 ± 4  | 7 ± 4  |
| PVRI (dynes·s/cm\(^5\) per m\(^2\)) | A     | 233 ± 103| 224 ± 67| 215 ± 66*| 242 ± 80|
|                           | B     | 240 ± 127| 285 ± 204| 264 ± 168| 277 ± 167|
| CVP (mmHg)                | A     | 3 ± 2  | 4 ± 2  | 3 ± 1  | 4 ± 2  |
|                           | B     | 2 ± 1  | 2 ± 1  | 2 ± 1  | 2 ± 1  |
| PaO\(_2\) (mmHg)          | A     | 80.3 ± 10| 74.6 ± 12| 71.6 ± 9*| 76.1 ± 12|
|                           | B     | 75.6 ± 12| 72 ± 13 | 71.8 ± 12| 71.3 ± 11|
| SaO\(_2\) (%)             | A     | 95.8 ± 1.5| 94.7 ± 2 | 94.2 ± 2*| 95 ± 2.4|
|                           | B     | 94.9 ± 2| 94.1 ± 2.4| 94.3 ± 2| 94.3 ± 2|
| PaCO\(_2\) (mmHg)         | A     | 38 ± 3 | 37 ± 3 | 38 ± 3 | 38 ± 3 |
|                           | B     | 37 ± 3 | 37 ± 5 | 37 ± 5 | 37 ± 4 |
| Qsp/Qt (%)                | A     | 12 ± 5 | 17 ± 6 | 18 ± 6*| 14 ± 8 |
|                           | B     | 15 ± 6 | 17 ± 8 | 17 ± 7 | 17 ± 6 |

\(^*P < 0.05,\) versus time point 1 within each group. See text for definitions of groups, subgroups and time points. CI, cardiac index; CVP, central venous pressure; HR, heart rate; MPP, mean pulmonary pressure; MSP, mean systemic pressure; PaCO\(_2\), arterial carbon dioxide tension; PaO\(_2\), arterial oxygen tension; PCWP, pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index; Qsp/Qt, shunt fraction; SaO\(_2\), arterial oxygen saturation; SVI, stroke volume index; SVRI, systemic vascular resistance index.
points 2 and 4 there were no significant changes in haemodynamic parameters as compared with time point 1.

Patients in group B and in subgroups A1, B1, and B2 did not show any significant haemodynamic change throughout the study (Tables 4 and 5). However, patients of subgroup A2 showed a significant increase \((P < 0.05)\) in heart rate (versus time point 2), CI and SVI, and a significant decrease \((P < 0.05)\) in SVRI and PVRI at time point 3 as compared with time point 1 (Table 4).

\(\text{PaO}_2\) and arterial carbon dioxide tension, arterial oxygen saturation and Qsp/Qt did not change significantly in patients of subgroups A1, B1, B2, and group B throughout the study (Tables 3–5). However, \(\text{PaO}_2\) and arterial oxygen saturation showed a significant reduction, and Qsp/Qt a significant increase at time point 3 as compared with time point 1 in patients of group A and subgroup A2 (Tables 3 and 4).

In the majority of cases studied pruritus was mild or moderate, and localized on the scalp, face, neck or upper torso. In a few cases it was severe and spread all over the body surface. In four cases pruritus was accompanied by a cutaneous rash, and no other clinical sign was observed.

### Discussion

The development of pruritus, an important symptom of histamine release, is relatively frequent with vancomycin administration \([2–4]\). It generally appears alone, but sometimes it is associated with headache; flushing; erythematous rash over the face, neck and upper torso (the so-called ‘red man’ syndrome); hypotension; and broncospasm \([4,13–15]\). One of the most important factors that impact on the incidence of these adverse reactions is the vancomycin infusion rate. For example, Renz and coworkers \([11]\) infused 1 g vancomycin over 10 min to patients scheduled for elective prosthetic joint replacement, and found that 90% of patients had rash and pruritus, and 50% had significant hypotension. Also, Valero and coworkers \([7]\) administered 1 g vancomycin over 30 min to cardiac surgical patients and observed hypotension in 25% of cases. For this reason, the international literature recommends that vancomycin be infused over a period of 60 min.
in order to prevent these side effects, and hypotension in particular, which in some cases manifests as life-threatening shock [6,8,9,16].

The present study was conducted to investigate the haemodynamic changes that occur following the appearance of pruritus. We therefore opted to administer vancomycin over a period of 30 min in order to encourage appearance of the sign, as the coronary patients were adequately monitored and the anaesthetist was therefore in the optimal conditions to detect and treat any change in cardiorespiratory function at an early stage.

Our analysis of haemodynamic profiles shows that, in those patients who exhibited pruritus (group A), systemic vascular resistance fell significantly 30 min after initiation of vancomycin administration. This effect was transient, disappearing 15 min later. The reduction in systemic vascular resistance was not accompanied by a significant decrease in systemic arterial pressure, and because heart rate was unchanged, the increase in stroke volume offset the peripheral vasodilatation induced by the antibiotic. On the contrary, in patients free from pruritus (group B), those haemodynamic changes were not observed and all of the parameters considered remained stable throughout the study. In group A the normovolaemic condition of the patients and the fluids infused during the study undoubtedly contributed to haemodynamic compensation. However, it may be supposed that if vancomycin is administered to an hypovolaemic patient then this compensation cannot be as effective and hypotension may occur. We were unable to confirm this for two reasons: first, hypovolaemia was among the exclusion criteria; and second, we considered exposure of a coronary patient to the additional stress of relative hypovolaemia to be harmful. However, considering the different amounts of crystalloid infused in each group, we can indirectly deduce that fluid compensation contributed to the maintenance of stable values for mean systemic pressure when systemic vascular resistance decreased.

The stability of heart rate in face of a reduction in systemic vascular resistance in group A patients renders possible an influence of preoperative β-blocker therapy on haemodynamic compensation. Confirmation of this is indicated by the different trends of heart rate in the group A patients who were treated with a β-blocker as compared with those who were

| Parameter          | Group | 1           | 2           | 3           | 4           |
|--------------------|-------|-------------|-------------|-------------|-------------|
| HR (beats/min)     | B1    | 62 ± 10     | 60 ± 12     | 62 ± 10     | 59 ± 9      |
|                    | B2    | 70 ± 10     | 67 ± 11     | 66 ± 12     | 66 ± 11     |
| MSP (mmHg)         | B1    | 90 ± 18     | 91 ± 20     | 91 ± 21     | 95 ± 20     |
|                    | B2    | 84 ± 18     | 83 ± 18     | 84 ± 20     | 86 ± 21     |
| SVRI (dynes/s/cm^5 per m^2) | B1 | 2511 ± 562  | 2623 ± 519  | 2392 ± 380  | 2607 ± 415  |
|                    | B2    | 2884 ± 1200 | 3021 ± 1600 | 2842 ± 1253 | 2980 ± 1160 |
| CI (l/min per m^2)  | B1    | 2.80 ± 0.5  | 2.69 ± 0.4  | 2.90 ± 0.5  | 2.70 ± 0.4  |
|                    | B2    | 2.46 ± 0.6  | 2.36 ± 0.6  | 2.49 ± 0.7  | 2.40 ± 0.6  |
| SVI (ml/beat per m^2) | B1 | 46 ± 10     | 46 ± 8      | 47 ± 7      | 46 ± 8      |
|                    | B2    | 36 ± 8      | 36 ± 9      | 38 ± 11     | 37 ± 10     |
| PVRI (dynes/s/cm^5 per m^2) | B1 | 218 ± 64    | 227 ± 76    | 253 ± 77    | 242 ± 96    |
|                    | B2    | 296 ± 183   | 365 ± 228   | 320 ± 197   | 332 ± 207   |
| PaO2 (mmHg)        | B1    | 75.3 ± 12   | 74.4 ± 13   | 73 ± 13     | 73 ± 12     |
|                    | B2    | 73.6 ± 13   | 72 ± 13     | 73.4 ± 10   | 70 ± 9      |
| SaO2 (%)           | B1    | 95 ± 2      | 94.5 ± 2    | 94.4 ± 2    | 94.7 ± 2    |
|                    | B2    | 94.5 ± 2    | 94 ± 2      | 94.6 ± 2    | 94 ± 2      |
| Qsp/Qt (%)         | B1    | 16 ± 7      | 17 ± 8      | 17 ± 7      | 16 ± 7      |
|                    | B2    | 16 ± 5      | 17 ± 6      | 16 ± 6      | 17 ± 4      |

No significant difference was observed within the two groups. See text for definitions of groups, subgroups and time points. CI, cardiac index; HR, heart rate; MSP, mean systemic pressure; PaO2, arterial oxygen tension; PVRI, pulmonary vascular resistance index; Qsp/Qt, shunt fraction; SaO2, arterial oxygen saturation; SVI, stroke volume index; SVRI, systemic vascular resistance index.
not. The stability of heart rate in subgroup A1 and the significant increase in subgroup A2 represents proof that \( \beta \)-blocker therapy limited that compensatory mechanism to peripheral vasodilatation. Surprisingly, assessment of other haemodynamic parameters (SVRI, CI, SVI) revealed a significant vasodilatation. Surprisingly, assessment of other haemodynamic parameters (SVRI, CI, SVI) revealed a significant vasodilatation. Surprisingly, assessment of other haemodynamic parameters (SVRI, CI, SVI) revealed a significant vasodilatation. Surprisingly, assessment of other haemodynamic parameters (SVRI, CI, SVI) revealed a significant vasodilatation. Surprisingly, assessment of other haemodynamic parameters (SVRI, CI, SVI) revealed a significant vasodilatation. Surprisingly, assessment of other haemodynamic parameters (SVRI, CI, SVI) revealed a significant vasodilatation. Surprisingly, assessment of other haemodynamic parameters (SVRI, CI, SVI) revealed a significant vasodilatation. Surprisingly, assessment of other haemodynamic parameters (SVRI, CI, SVI) revealed a significant vasodilatation. Surprisingly, assessment of other haemodynamic parameters (SVRI, CI, SVI) revealed a significant vasodilatation. Surprisingly, assessment of other haemodynamic parameters (SVRI, CI, SVI) revealed a significant vasodilatation. Surprisingly, assessment of other haemodynamic parameters (SVRI, CI, SVI) revealed a significant vasodilatation. Surprisingly, assessment of other haemodynamic parameters (SVRI, CI, SVI) revealed a significant vasodilatation. Surprisingly, assessment of other haemodynamic parameters (SVRI, CI, SVI) revealed a significant vasodilatation. Surprisingly, assessment of other haemodynamic parameters (SVRI, CI, SVI) revealed a significant vasodilatation. Surprisingly, assessment of other haemodynamic parameters (SVRI, CI, SVI) revealed a significant vasodilatation. Surprisingly, assessment of other haemodynamic parameters (SVRI, CI, SVI) revealed a significant vasodilatation. Surprisingly, assessment of other haemodynamic parameters (SVRI, CI, SVI) revealed a significant vasodilatation. Surprisingly, assessment of other haemodynamic parameters (SVRI, CI, SVI) revealed a significant vasodilatation. Surprisingly, assessment of other haemodynamic parameters (SVRI, CI, SVI) revealed a significant vasodilatation.

The significant increase in \( Qsp/Qt \) and decrease in \( PaO_2 \) in the patients affected by pruritus can be interpreted as the effect of an imbalance in the ventilation/perfusion ratio, induced by the vasodilating action of vancomycin on the pulmonary circulation, as supported by the significant reduction in pulmonary vascular resistance at time point 3. Also, the respiratory changes were significant only in patients of group A who were not treated with a \( \beta \)-blocker, whereas preoperative use of the drug eliminated any significant respiratory change. The degree of reduction in \( PaO_2 \) was moderate and had no important impact on arterial haemostasis in the patients studied, who showed however normal preoperative respiratory function.

A limitation in the calculation of \( Qsp/Qt \) was that the patients were breathing room air during the study. In such conditions, apart from changes in the \( Qsp/Qt \), the decrease in \( PaO_2 \) may be caused by effects of maldistribution in the ventilation/perfusion ratio. For this reason we must consider the \( Qsp/Qt \) not as an absolute value but as a relative one, but we can nevertheless attribute meaning to changes in this parameter [12].

On the basis of the results obtained, we conclude that occurrence of pruritus during vancomycin administration must be considered an alarm bell that indicates the presence of peripheral vasodilatation. It can help the physician to identify at an early stage those patients who are at risk for hypotension (e.g. hypovolaemic patient) and to compensate for hypovolaemia before continuing administration of vancomycin. This benefit is useful not so much in intensive care units (where patients are continuously and adequately monitored) as in medical and surgical departments overall, where monitoring of arterial pressure is not continuous and nurse care is not as strict as in the intensive care unit.

Finally, the lack of haemodynamic and respiratory changes in the patients affected by pruritus and treated with a \( \beta \)-blocker before surgery makes it probable that these agents can confer protection against the anaphylactoid reactions that are mediated by release of histamine.

**Competing interests**

None declared.

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