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LETTER

Vancomycin trough level and loading dose

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Dear editor

We read with interest the paper by Barceló-Vidal et al[1] about vancomycin nephrotoxicity due to high trough levels with histopathology. The authors described a case developing both lesions and described total vancomycin washout after a biopsy-proven vancomycin toxicity. Unfortunately, most patients receiving the loading dose of >25 mg/kg do not achieve adequate trough level, which was recommended by some guidelines to be between 15 and 20 mg/L.[2] Considering this issue, we performed a brief study in two Brazilian hospitals with therapeutic drug monitoring (TDM) of vancomycin and loading dose of 30 mg/kg. The inclusion criteria for the retrospective observational study were as follows: patients were aged >18 years, admitted to an intensive care unit (ICU), with infection, and received at least 72 hours of vancomycin, with the creatinine level of <1.5 mg/dL in the first day of vancomycin.

All patients received 30 mg/kg of loading dose, and vancomycin trough level was obtained before the fifth dose. In obese patients, the dose was according to adjusted body weight. Vancomycin was prescribed with intermittent dose of 15 mg/kg every 12 hours. The following outcomes were analyzed: all-cause mortality, acute kidney injury (AKI), and trough level <15 mg/L. AKI was classified according to Acute Kidney Injury Network (AKIN) criteria.[3] Risk factors were calculated according to the variable and its distribution and considered statistically significant when there was a difference of <5% ($P<0.05$). For the multivariate analysis, all variables with statistical significance in the univariate analysis were included in a binary logistic regression.

Results from 164 patients are summarized in Table 1. Trough level was >15 mg/L in 76.8% (n=126). Only 13.4% (n=22) achieved the "ideal level" (15–20 mg/L); however, 18.9% (n=31) achieved levels between 20 and 30 mg/L and 44.5% (n=69) achieved levels higher than 30 mg/L. No risk factor was associated with lower/higher levels of vancomycin. Nevertheless, age, concomitant use of aminoglycoside, systemic arterial hypertension, and vancomycin trough level >30 mg/L were associated with AKI. Vancomycin trough level of >30 mg/L was an independent risk factor for AKI. The all-cause mortality was 44.5%. The risk factor associated with death in the final model of multivariate analysis was AKI, and vancomycin trough level was >30 mg/L.

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Table 1 Clinical, laboratorial and outcome data of patients treated with vancomycin

Variables	Total		AKI		Without AKI		
	N=164	%	N=74	%	N=90	%	*P*-value
Female	69	42.1	35	21.3	34	20.7	0.219
Death	73	44.5	45	27.4	28	17.1	0.001
Aminoglycoside	28	17.1	18	11	10	6.1	0.025
Polymyxin	32	19.5	18	11	14	8.5	0.159
Previous admission in ICU	4	2.4	2	1.2	2	1.2	0.843
HIV	5	3	2	1.2	3	1.8	0.815
Diabetes	22	13.4	12	7.3	10	6.1	0.34
Previous myocardial infarction	14	8.5	8	4.9	6	3.7	0.345
Congestive heart failure	10	6.1	6	3.7	4	2.4	0.329
Peripheral vascular disease	15	9.1	8	4.9	7	4.3	0.503
Cerebrovascular disease	21	12.8	11	6.7	10	6.1	0.474
Dementia	6	3.7	5	3	1	0.6	0.055
Chronic pulmonary disease	11	6.7	4	2.4	7	4.3	0.546
Systemic arterial hypertension	77	47	42	25.6	35	21.3	0.023
Neoplasm	18	11	7	4.3	11	6.7	0.573
Previous corticoid therapy	4	2.4	1	0.6	3	1.8	0.413
Immunosuppression	9	5.5	3	1.8	6	3.7	0.465
Trauma	44	26.8	17	10.4	27	16.5	0.312
Emergency surgery	16	9.8	8	4.9	8	4.9	0.68
Elective surgery	60	36.6	29	17.7	31	18.9	0.53
Serum level of vancomycin >30 mg/L	91	55.5	30	18.3	61	37.2	0.001
Age (mean ± SD) (years)	56.1	19.5	61.4	18.4	52.0	19.4	0.002
Hospitalization (mean ± SD)	35.8	25.1	34.6	23.8	36.8	26.2	0.583
Charlson (mean ± SD)	1.2	1.6	1.2	1.4	1.2	1.8	0.967
Cr admission (mean ± SD)	1.1	1.3	1.1	1.0	1.0	1.6	0.644
Cr, first day of vancomycin (mean ± SD)	0.7	0.4	0.7	0.4	0.6	0.3	0.302
First vancomycin serum level (mean ± SD)	29.9	17.5	34.7	17.5	26.0	16.6	0.001

Abbreviations: AKI, acute kidney injury; Cr, creatinine; ICU, intensive care unit.

After reading the paper by Barceló-Vidal et al,[1] we also performed an analysis of patients with vancomycin trough level of >60 mg/L. From 164 patients, six had vancomycin trough level of >60 mg/L, and 50% (3/6) had severe AKI (AKIN 3): OR=5.38 (95% CI: 1.02–27.87; $P<0.05$).

Higher loading dose of vancomycin is necessary to achieve ideal therapeutic level of vancomycin. Unfortunately, this approach has the consequence of higher rates of AKI, which increases mortality. The only modifiable risk factor for AKI was vancomycin trough level of >30 mg/L. At this aspect, we should discuss alternatives to vancomycin in severe AKI patients or assume the consequences of ideal therapeutic levels with more AKI.

Disclosure

Felipe Francisco Tuon is a Conselho Nacional de Pesquisa (CNPQ) researcher. The other authors report no conflicts of interest in this communication.

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Authors' reply

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Dear editor

We read with interest the study by Tuon et al about the loading dose and therapeutic drug monitoring (TDM) of vancomycin in patients in intensive care units (ICUs). In the study, the authors highlight the significance to perform TDM in patients receiving vancomycin, since <15% of their patients achieved ideal levels. On the other hand, >60% of these patients had supratherapeutic levels. In addition, all-cause mortality had a high percentage. These results are alarming, and the authors conclude that some alternatives to vancomycin should be given to severe patients, but these patients can also benefit from this antibiotic as long as their use and monitoring are optimized.

Although the loading dose of 30 mg/kg was according to adjusted body weight in obese patients included in the reference study, the obese criteria in these patients are not defined. Moreover, it is known that not only obese patients but also those who are overweight (body mass index 25–30 kg/m^2) can be overdosed when the loading dose of vancomycin is calculated according to the total body weight.[1] Furthermore, patients' demographics such as weight should also be described in the table, since it would be interesting to know the mean weight of this population.

In relation to the all-cause mortality rate and considering ICU patients, it is necessary to have a severity score such as APACHE II/III or SOFA and not just a Charlson score, which is actually a comorbidity index and its representation about critically ill patients is limited.[2,3] Moreover, the authors describe severe acute kidney injury (AKI) in 50% of patients with vancomycin trough level of >30 µg/mL, and AKI was associated with all-cause mortality rate. Considering critically ill patients, there are no data available on renal function evolution; probably, the best way to avoid this AKI is daily monitoring of renal function (serum creatinine, glomerular filtration rate, and need of hemodialysis) and adjusting vancomycin dosage depending on these variables.

In the study, following the latest recommendations from the *Infectious Diseases Society of America* (IDSA; 2009), a trough level of 15–20 µg/mL is considered to be the "ideal level". Nevertheless, recent studies have described that TDM of vancomycin using the pharmacokinetic/pharmacodynamic (PK/PD) parameter area under the curve/minimal inhibitory concentration (AUC/MIC) has the same clinical outcomes regarding effectiveness as the trough method, but presented less incidence of AKI. Based on these results, TDM of vancomycin should take the lead to obtain these PK/PD parameters and try to achieve an AUC/MIC of 400–700 µg/mL×h since the trough method could lead to greater AUC values, which could be produced in a higher rate of AKI.[4,5]

Finally, it would be interesting if more information could be obtained about these patients with trough values of >60 µg/mL if the kind of kidney injury is similar to our case, and also about the time it took for these patients to have undetectable vancomycin levels.

Disclosure

The authors report no conflicts of interest in this communication.

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