A Comparison of Nephrotoxicity in Non–Intensive Care Unit Medical/Surgical Patients Receiving Vancomycin Alone Versus Vancomycin With Piperacillin-Tazobactam—Do We Need to Ban This Combination ?

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Written as an editorial commentary regarding Eberle et al. A Comparison of Nephrotoxicity in Non–Intensive Care Unit Medical-Surgical Patients Receiving Vancomycin Alone Versus Vancomycin With Piperacillin-Tazobactam *pages 23–26 of the Journal.*

Eberle et al[1] from Regional One Health in Memphis, Tennessee, publish in this issue of the journal a study where they examined whether associating piperacillin/tazobactam to vancomycin will increase nephrotoxicity of this old but still widely trusted glycopeptide. The study, which is retrospective and from a single institution, enrolled 198 evaluable patients (out of a total of 867 retained in a first round of selection) over a period of 6 months in 2015 to 2016. The results are straightforward, with vancomycin-attributable nephrotoxicity rising from 5.6% to 18.4% when comparing patients receiving vancomycin only versus those with combination therapy.[1]

The strengths of the study are as follows: (1) only patients from medical and surgical populations in non–intensive care units were included, thus avoiding many of the complexities and confounding factors associated with more severe patients; and (2) very few patients received other known nephrotoxins, making the association of renal toxicity to the antibiotics under study somewhat more likely.

Vancomycin nephrotoxicity, and how clinical signs of renal failure can be ascribed to this drug, remains a difficult question to address. First, and in spite of large efforts, the underlying molecular and cellular mechanisms of vancomycin nephrotoxicity remain largely elusive, going from such disparate possibilities as selective transport through the basolateral membrane, lysosomal accumulation, mitochondrial dysfunction, and oxidative stress.[2,3] Moreover, although animal[4,5] as well as more recent human biopsy studies (see, eg, Refs.[6–8]) tend to reveal tubular necrosis as a first definite histopathological alteration after exposure to vancomycin, clinicians rely mostly, as in this study, on a "≥50% increase in serum creatinine" criterion, which is essentially a marker of glomerular dysfunction and is very insensitive to detect mild changes in renal functions and to explore the temporal cause-to-effect relationships in toxicity.[2,3] The situation is made even more complex by the fact that the rates of vancomycin attributable nephrotoxicity vary between studies from almost 0% to more than 40%, suggesting key roles for multifactorial factors in triggering clinically detectable effects. Among the most established risk factors are the following: (1) those related to vancomycin itself, such as the total dose, elevated trough levels (but these may a consequence as well as a cause of renal failure, since the drug is primarily eliminated by the renal route), and the duration of treatment (toxicity becoming significant only after 4–6 days of treatment); and (2) those related to patient's factors or concomitant administered drugs. It is in the latter context that the Eberle et al's[1] study must be considered. The data pertain to patients with no other known nephrotoxin, making piperacillin/tazobactam the most likely culprit.

The pejorative effect of coadministering piperacillin/tazobactam and vancomycin has been described for many years and is the subject of a large number of convergent reports,[9–12] including some very recent, and sometimes with a very large number of patients, which the authors may not have had access to.[13–19] Others, however, did not find such an aggravating effect of piperacillin/tazobactam while examining a population of a similar size to that of Eberle et al.[20,21] Interestingly enough, one group of authors arrived to different conclusions when reporting their own data (no detrimental effect[20]) and when performing a large meta-analysis (3.11 odd ratio is disfavor of piperacillin/tazobactam coadminsitration[12]). Possibly, random effects and inherent differences between patient populations may explain these divergences. More basic difficulties also stem from the fact that no study directly addressed the underlying mechanisms of an enhanced toxicity (apart from general considerations concerning the ability of piperacillin/tazobactam to cause acute interstitial nephritis,[22] but this is seen with other β-lactams) and whether the culprit is piperacillin or tazobactam.

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Nevertheless, by and large, we can probably accept the idea that administration of piperacillin/tazobactam is a risk factor for causing increased nephrotoxicity with vancomycin.

The question, then, is to know what needs to be done with that in the clinics. Assuming that prescribing piperacillin/tazobactam is rational (ie, based on its anticipated activity against causative Gram-negative organisms, including *Pseudomonas aeruginosa*), several alternatives exist within the β-lactam class, such as ceftazidime, cefepime, carbapenems, or even ceftolozane/tazobactam (assuming tazobactam is not the cause of the problem), as well as in other classes, such as that of fluoroquinolones and aminoglycosides. Nevertheless, each of these alternatives has its own therapeutic and toxicity issues (for instance, aminoglycosides definitely enhance vancomycin nephrotoxicity[3,4]). Thus, we may easily be moving from Scylla to Charybdis and do more harm than good. If Gram-positive organisms is the target, we may get rid of vancomycin and try selecting another agent. Thus, the first safe move would be to check whether a more benign drug, such as an antistaphylococcal penicillin (nafcillin or oxacillin) could not do the job. If not, we have now a large array of seminovel and novel anti–Gram-positive antibiotics, such as daptomycin (lipopeptide); ceftaroline (an anti–methicillin-resistant *Staphylococcus aureus* cephalosporin); telavancin, oritavancin, and dalbavancin (lipoglycopeptides); linezolid and tedizolid (oxazolidinones); and even delafloxacin (a recently approved fluoroquinolone with very low minimum inhibitory concentrations against *S. aureus*, including methicillin-resistant ones), which are all active against most of the bacteria usually targeted by vancomycin. The questions, here, are at several levels of variable importance depending from the environment and the way we treat patients. For instance, do we wish our patients to go home faster (by reducing the number of injections [favoring, eg, oritavancin or dalbavancin] or by an easy switch to oral administration [selecting linezolid or tedizolid])? Or, would not some patients be at a particular risk of toxicity with an alternative drug (for instance, the risk linezolid-associated thrombocytopenia is enhanced by renal failure,[23,24] and the high doses of daptomycin necessary in salvage therapy may cause a high level of eosinophilic pneumonia[25])? Also, are we prepared to use some these drugs off-label (as their approved indications are, so far, often very limited)? Lastly, can we economically afford these new drugs?

Thus, we are probably to live with the fact that piperacillin/tazobactam creates a risk of increased vancomycin nephrotoxicity and take every measure we can to protect our patients, while avoiding unnecessary changes in our current antibiotic armamentarium (if effective against the organisms we fight). This may be all the more important as vancomycin-induced nephrotoxicity is reversible, even sometimes without removing the drug from the patient's regimen.[3] Nevertheless, we should continue to check for alternatives to both vancomycin (which may become less consistently effective as minimum inhibitory concentrations rise above 1.5 mg/L[2,3]) and to piperacillin/tazobactam, but remembering that *primum non nocere* must remain our motto.

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