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Lack of Synergistic Nephrotoxicity in a Mouse Model of Vancomycin-Induced AKI with Piperacillin-Tazobactam Coadministration

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Vancomycin (VN) and piperacillin-tazobactam (PT) are two antibiotics commonly used in combination to provide broad antibacterial coverage in patients hospitalized for serious infections. VN is known to confer a high risk of AKI, whereas PT is not known to be nephrotoxic as a single agent, except rare reports of acute interstitial nephritis.¹ Several recent observational studies and meta-analyses suggest that this antibiotic combination increases the risk of AKI.² Consequently, in 2017, the US Food and Drug Administration and other regulatory bodies cautioned against using this combination as empirical treatment.³ However, the mechanism of this potential interaction remains unknown. In addition, a recent clinical study suggests that PT inhibits tubular creatinine secretion when used in combination with VN, which may have biased the conclusions of meta-analysis.⁴

Given the key role of combining PT and VN in the treatment of life-threatening infections, the emergence of evidence regarding this nephrotoxic synergy is a major challenge. Therefore, the aim of this study was to investigate whether there is synergistic nephrotoxicity between VN and PT using an experimental model of VN-induced AKI in mice.⁵

We have previously described a mouse model of VN-induced AKI and demonstrated a novel mechanism of VN nephrotoxicity due to intratubular cast formation. However, we did not find any difference in kidney function in mice injected with VN or VN+PT.⁵ Given the severity of the original model, any potential synergistic nephrotoxicity might have been masked by the severity of renal damage. Thus, in these new studies, we first administered male C57BL/6 mice (8–9 weeks old) with incremental doses of VN once a day for 2 days and collected blood and kidney samples on day 3. We observed that VN-induced AKI,

as reflected by plasma urea levels, is dose-dependent (Figure 1A). Based on these results, the dose of 0.5 mg/g per day of VN was chosen to induce moderate AKI and investigate the potential synergistic effect of the VN+PT combination.

Mice received either saline, PT, VN, or VN+PT for 2 days. PT was injected intraperitoneally at 0.1 mg/g per day, as previously described.⁵ On day 3, mice receiving VN or VN+PT demonstrated a fall in kidney function compared with the saline and PT groups, but no difference was observed between the two groups (Figure 1B). VN and VN+PT groups showed a similar reduction in transdermal measured GFR on day 3 (Figure 1C). Similarly, renal expression of kidney injury molecule-1 (KIM-1) mRNA, acute tubular necrosis score, and tubular cast score were increased in the VN and VN+PT groups with no difference between these two groups (Figure 1, D–F). These data suggest that PT does not worsen VN-induced AKI in our mouse model.

We then studied the combination of VN with high doses of PT (PTHD) to understand if the previous PT dose was insufficient to induce synergistic nephrotoxicity. PTHD was injected subcutaneously to avoid intraperitoneal precipitation as has been reported⁶ at 2.5 mg/g per day to approach the maximum human dose following allometric scaling for mice. On day 3, plasma urea was higher in the VN group than in the PTHD and VN+PTHD groups. Renal KIM-1 mRNA, acute tubular necrosis score, and tubular cast score were higher in the VN and VN+PTHD groups but with no between-group differences (Figure 1G). Finally, we performed intravital microscopy in mice receiving VN or VN+PTHD to observe the *in vivo* VN obstructive tubular cast formation using a VN-boron-dipyrromethene-associated dye. We observed that casts

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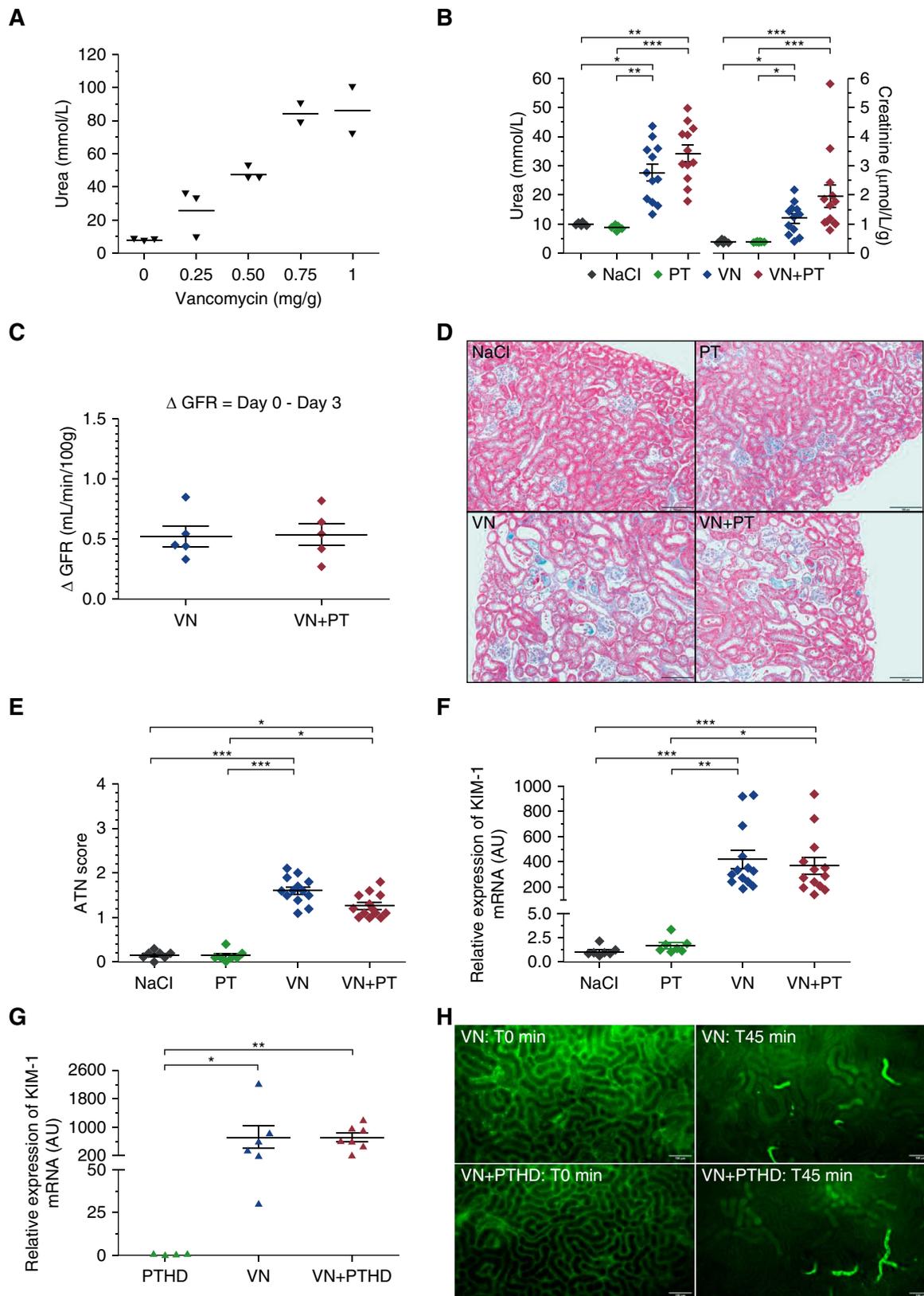


Figure 1. VN dose-dependent effect on nephrotoxicity and impact of the combination of VN and PT. (A) Plasma urea levels measured after injection of increasing doses of VN. One mouse died in the 0.75 mg/g group and one in the 1 mg/g group. (B) Plasma urea levels measured after injection of saline (NaCl) ($n=7$), PT ($n=7$), VN ($n=12$), or VN+PT ($n=12$). (C) Changes in GFR in VN and VN+PT groups. (D) Histological lesions observed with Masson trichrome, scale bar: 100 μm . (E) ATN evaluation score: 0, no injury; 1, 1%–25% injury; 2, 26%–50% injury; 3, 51%–75% injury; 4, 76%–100% injury. For each section, ten fields were evaluated and the average of these ten fields was calculated. (F)

Figure 1. *Continued.* Relative renal expression of KIM-1 mRNA quantified by RT-qPCR. (G) Relative renal expression of KIM-1 mRNA quantified by RT-qPCR after injection of high doses of PT (PTHD) ($n=4$), VN ($n=6$), or VN+PTHD ($n=7$). (H) *In vivo* formation of VN-associated tubular casts 45 minutes after injection of dye-linked VN (boron-dipyrromethene) alone and after 48 hours of exposure to PTHD, scale bar: 100 μm . * $P < 0.05$; ** $P < 0.001$; *** $P < 0.0001$. ATN, acute tubular necrosis; KIM-1, kidney injury molecule-1; PTHD, high doses of piperacillin-tazobactam; PT, piperacillin-tazobactam; VN, vancomycin.

appeared rapidly after VN injection and were easily detectable after 45 minutes, but there was no difference in cast formation between the two groups (Figure 1H).

In this study, we have validated systemic injection of VN as a dose-dependent preclinical model of tubular AKI and showed that concomitant administration of PT does not aggravate its nephrotoxicity. Although previous meta-analyses have suggested a synergistic nephrotoxicity of these two antibiotics, the mechanism for this was unknown. Miano *et al.* suggest that PT inhibits tubular secretion of creatinine without inducing nephrotoxic synergy.⁴ Interestingly, our results reveal a dissociation trend between plasma creatinine and plasma urea when comparing the VN and VN/PT groups, which could support that mechanistic hypothesis. However, a larger sample size would be necessary to confirm it.

A recent randomized clinical trial compared PT with cefepime in patients hospitalized for suspected sepsis. In this trial, over 80% of patients received at least one dose of VN, and there was no difference in the incidence of AKI between the VN+PT and VN+cefepime groups.⁷ Despite its limitations, this study provides the strongest clinical evidence against a nephrotoxic synergy between VN and PT. In addition, other preclinical data provide additional evidence against nephrotoxic synergy.^{2,5,6} As in our study, there was neither an increase in KIM-1 nor a greater decrease in GFR with the VN+PT combination.

We recognize the limitations of this work including the ability of animal models to reproduce human pathology. However, human data are generally difficult to analyze in the context of drug toxicity because of significant confounders. Unfortunately, current guideline suggestions to avoid the PT/VN combination are based on these sorts of analyses. Our mouse model—which does not suffer from other nephrotoxic confounders—fails to show any increase in kidney injury when PT and VN are coinjected. Although previous meta-analyses suggested nephrotoxic synergy, recent clinical trials and preclinical data contradict this, challenging current recommendations to avoid the PT/VN combination in life-threatening infections.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at <http://links.lww.com/KN9/A476>.

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Data Sharing Statement

All data are included in the manuscript and/or supporting information.

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