Piperacillin–Tazobactam Plus Vancomycin-Associated Acute Kidney Injury

Subjects: Infectious Diseases

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Numerous observational studies and meta-analyses have suggested that combination therapy consisting of piperacillin–tazobactam (TZP) and vancomycin (VAN) augments acute kidney injury (AKI) risk when compared to viable alternatives, such as cefepime–vancomycin (FEP–VAN) and meropenem–VAN.

piperacillin–tazobactam vancomycin teicoplanin

1. Introduction

Acute kidney injury (AKI) has been observed in up to a quarter of hospitalized patients and is associated with excess mortality and morbidity [1]. As a risk factor for the development of AKI in these patients, antibiotics undoubtedly play a critical role with the main offending agents, such as acyclovir, amphotericin B, aminoglycosides, colistin, and vancomycin (VAN) [2][3]. The relationship between AKI and VAN exposure has been known for a long time and was initially the result of impurities in early formulations. Owing to the technical developments in drug manufacturing, the increased nephrotoxicity risk related to early VAN formulations was eventually eliminated [4]. Nevertheless, nephrotoxicity may be augmented with several drug combinations, including piperacillin–tazobactam (TZP) plus VAN for which the incidence of AKI has been reported within a range of 5.5% to 46.0% [5]. Besides a TZP–VAN combination regimen, high VAN trough levels, concurrent exposures to other nephrotoxic medications, long duration of VAN therapy (>7 days), the severity of illness, underlying kidney dysfunction, obesity, and ICU admission are other relevant risk factors for VAN-related AKI [6]. From a pathophysiological point of view, VAN-associated AKI can be mediated by proximal tubular injury, interstitial nephritis, and cast nephropathy [7][8]. However, the mechanisms underlying the synergistic nephrotoxic interaction between TZP and VAN are still unclear.

Many retrospective cohort studies and meta-analyses have demonstrated that TZP plus VAN is associated with a higher risk of AKI than those of other VAN plus β-lactam combinations [9][10][11][12]. In a meta-analysis that included 14 observational studies, concomitant use of VAN and TZP was reported as a risk factor for increased AKI (p = 0.001). Intriguingly, a higher risk of AKI was detected only in those studies in which the ratio of patients receiving antibiotic therapy in ICUs was <50% (in adjusted analysis OR, 3.04; 95% CI, 1.49–6.22; p = 0.002) [13]. Similarly, another recent systematic review and network meta-analysis reported that the TZP–VAN combination was significantly more nephrotoxic than VAN alone or VAN in combination with meropenem (MER) or cefepime (FEP) [12].

As another parenteral glycopeptide antibiotic, teicoplanin (TEI) can well be used in place of VAN in many indications and it is widely available worldwide, including in Europe, the Middle East, and Asia-Pacific, but not in the US [14]. Previous studies comparing TEI and VAN usually indicated a safer nephrotoxicity profile with the former antibiotic [15]. In a Cochrane systematic review and meta-analysis, 24 randomized controlled trials that included 2610 patients with proven or suspected Gram-positive infections, TEI had a lower risk of nephrotoxicity than VAN (RR, 0.66; 95% CI, 0.48–0.90; I^2 = 10%) and no patient required dialysis in either TEI or VAN group. Furthermore, clinical cure and microbiological eradication rates were similar to TEI and VAN (RR, 1.03; 95% CI, 0.98–1.08; I^2 = 0%). However, the randomized controlled trials included in this meta-analysis were small and most of the studies had methodological problems. Therefore, the quality of the evidence regarding the risk of AKI of TEI compared to that of VAN was assessed as moderate according to the GRADE system [16].

2. Epidemiology of TZP Plus VAN-Associated AKI

For the first time in the literature, the risk of AKI related with the TZP–VAN combination regimen was reported in 2011 [17]. Since then, contemporary literature has been inundated with a deluge of observational studies comparing the AKI risk of TZP–VAN with either those of VAN alone or VAN plus other antipseudomonal β-lactam agents. The TZP plus VAN combination provides a wide spectrum of activity against methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterobacterales*, *Enterococcus* spp., *Pseudomonas aeruginosa*, and anaerobes; thus, the combination is typically used as empirical therapy in patients who are at risk of infections caused by these pathogens. TZP can be substituted with other antipseudomonal β-lactams, including meropenem for the same indications. In this regard, a large number of observational studies have been published comparing the rates of AKI seen in patients receiving TZP–VAN and those treated with FEP–VAN or MER–VAN. It should be noted that these studies minimize the confounding by indication that is typical when the comparator group comprises patients receiving VAN monotherapy. The results of the studies are summarized in **Table 1** [9][10][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41]. According to these studies, patients treated to the TZP–VAN combination regimen are 1.2–9.5 times more likely to develop AKI compared to those receiving FEP–VAN or MER–VAN combinations. However, these results should be cautiously evaluated due to following reasons: (I) the presence of significant heterogeneity between the comparison groups in terms of baseline characteristics of recruited patients, (II) differences in criteria used to define AKI, (III) different comparison groups (e.g., TZP–VAN vs. FEP–VAN), (IV) variations in the level of VAN exposure, (V) percentage of critically ill patients in the whole cohort, (VI) number of other nephrotoxic agents received, (VII) sample size of the studies, (VIII) statistical methodologies being used, (IX) percentage of patients with baseline kidney dysfunction within the entire cohort. In addition, although some studies performed multivariate analyses and propensity score–matched analyses, the impacts of other confounding factors not taken into account and selection bias could not be eliminated completely. Moreover, in the vast majority of the studies, since the data collections were done retrospectively and extracted in a nonblinded manner from the electronic patient records in single institutions, no causal relationships can be established. In some studies, the details of the patients' records do not allow for evaluation of each potential risk factor for AKI, such as the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, hypovolemia, hypoalbuminemia, VAN serum level, and hypotension. Moreover, the impacts of multiple generic products of

antibiotics on the AKI risk should not be underestimated. Because of the retrospective nature of the studies, urine output could not be assessed for the AKI definition, which may affect the rates of AKI. Finally, in some studies, the nephrotoxic potentials of the agents were thought to be the same, but this is not true. Furthermore, the dual representation of nephrotoxic exposure does not explain the duration and dose of agents taken over the course of treatment. Therefore, this approach cannot reflect the actual exposure to other nephrotoxic agents.

Table 1. Studies comparing the rate of AKI with piperacillin–tazobactam plus vancomycin and meropenem or cefepime plus vancomycin.

Authors and Type	Year	Country	Population	Definition of AKI *	ICU Residence and/or Critically Ill, %	Sample Size, *n*	Exposure to Other Nephrotoxins, %	Mean or Initial VAN Trough Level (mg/dl)	Treatment Duration, Days	Comparison Groups	Rate of AKI
Moenster RP, et al. R, SC, [18]	2014	USA	Adult patients with or without renal dysfunction	RIFLE	Not provided	139	Yes, percentage unknown	15.8 vs. 14.5	14.7 vs. 11.3	TZP–VAN vs. FEP–VAN	29.3% vs. 13.3%; OR, 3.45 (0.96–12.4); *p*: 0.05
Gomes DM, et al. R, SC, [19]	2014	USA	Adult patients without renal dysfunction	AKIN	34.8 vs. 53.6	224	Yes, percentage unknown	14.1 vs. 13.06	7.1 vs. 6.7	TZP–VAN vs. FEP–VAN	34.8% vs. 12.5%; OR, 3.74 (1.89–7.39); *p*: <0.001
Hammond DA, et al. R, SC, [20]	2016	USA	Adult patients without renal dysfunction	AKIN	100	122	Yes, percentage unknown	17.9 vs. 15.1	Not provided	TZP–VAN vs. FEP–VAN	32.7% vs. 28.8%; *p*: 0.76
Al Yami MS, et al. R, MC, [21]	2017	Saudi Arabia and USA	Adult patients without renal dysfunction	KDIGO	17.6 vs. 17.3	183	62.9 vs. 46.6	15.7 vs. 16.9	4.3 vs. 5.4	TZP–VAN vs. MER–VAN	7.4% vs. 5.3%; *p*: 0.4
Rutter WC, et al. R, SC, [9]	2017	USA	Adult patients with or without renal dysfunction	RIFLE	Not provided	4193	60.7 vs. 59.4	Percentage of >20 mg/L 30.4% vs. 27.4%	3.0 vs. 4.0	TZP–VAN vs. FEP–VAN	21.4% vs. 12.5%; OR, 2.18 (1.64–2.94); *p*: < 0.001

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Jeon N, et al. R, SC, [22]	2017	USA	Adult patients with or without renal dysfunction	KDIGO	14.09 vs. 18.75	5335	Yes, percentage unknown	Percentage of >20 mg/L 2.5% vs. 1.9%	5.0 vs. 5.0	TZP–VAN vs. FEP–VAN	19.6% vs. 16.2%; aHR, 1.25 (1.11–1.42); *p*: < 0.05
Navalkele B, et al. R, SC, [23]	2017	USA	Adult patients without renal dysfunction	RIFLE and AKIN	21 vs. 23	558	Yes, percentage unknown	17.3 vs. 17.7	Not provided	TZP–VAN vs. FEP–VAN	29% vs. 11%; HR, 4.27 (2.73–6.68); *p*: <0.001
Peyko V, et al. P, SC, [24]	2017	USA	Adult patients with or without renal dysfunction	KDIGO	Not provided	85	33.9 vs. 38.5	16.6 vs. 18.3	Not provided	TZP–VAN vs. MER–VAN or FEP–VAN	37.3% vs. 7.7%; *p*: 0.005
Cannon JM, et al. R, SC, [25]	2017	USA	Adult patients without renal dysfunction	RIFLE	15.8 vs. 31.1	366	Yes, percentage unknown	Percentage of >20 mg/L 21.9% vs. 28.4%	Not provided	TZP–VAN vs. MER–VAN	25.3% vs. 9.5%; *p*: 0.008
Clemmons AB, et al. R, SC, [26]	2018	Georgia	Adult patients with or without renal dysfunction	KDIGO	Not provided	170	Not provided	Percentage of >20 mg/L 42.9% vs. 31.6%	4.0 vs. 4.0	TZP–VAN vs. FEP–VAN	68% vs. 27%; OR, 5.1 (2.5–10.5); *p*: < 0.001
Mullins BP, et al. P, MC, [27]	2018	USA	Adult patients without renal dysfunction	RIFLE	34 vs. 41	242	Yes, percentage unknown	16.3 vs. 15.2	5.4 vs. 6.4	TZP–VAN vs. MER–VAN or FEP–VAN	29.8% vs. 8.8%; OR, 6.6 (2.8–15.8), *p*: <0.001
Robertson AD, et al. R, SC, [28]	2018	USA	Adult patients without	RIFLE	0	169	81.2 vs. 83.3	Percentage of >20 mg/L	4.6 vs. 4.7	TZP–VAN vs. MER–VAN	16.5% vs. 3.6%; OR, 6.8 (1.5–

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			renal dysfunction					21.2% vs. 19.0%			0.9); *p*: 0.009
Balcı C, et al. R, SC, [29]	2018	Turkey	Adult patients with or without renal dysfunction	AKIN	Not provided	132	52.8 vs. 65.2	Not provided	Not provided	TZP–VAN vs. MER–VAN	41.3% vs. 10.1%; OR, 0.33 (0.21–0.77); *p*: <0.001
Buckley MS, et al. R, SC, [30]	2018	USA	Adult patients with or without renal dysfunction	RIFLE	100	333	Yes, percentage unknown	13.5 vs. 13.1	5.1 vs. 5.8	TZP–VAN vs. FEP–VAN	19.5% vs. 17.3%; OR, 0.86 (0.49–1.53); *p*: 0.6
Rutter WC, et al. R, SC, [10]	2018	USA	Adult patients with or without renal dysfunction	RIFLE	Not provided	10,236	Yes, percentage unknown	Not provided	5.0 vs. 5.0	TZP–VAN vs. MER–VAN	27.4% vs. 15.4 %; OR, 2.53 (1.82–3.52); *p*: < 0.001
Ide N, et al. R, SC, [31]	2019	Japan	Adult patients with or without renal dysfunction	KDIGO	0	82	Yes, percentage unknown	Percentage of >15 mg/L 52.0% vs. 50.0%	Not provided	TZP–VAN vs. MER–VAN	33.3% vs. 9.1%; *p*: 0.015
Schreier DJ, et al. R, SC, [32]	2019	USA	Adult patients with or without renal dysfunction	AKIN	100	3299	Yes, percentage unknown	Not provided	All patients received 24-72 h combination therapy	TZP–VAN vs. MER–VAN vs. FEP–VAN	1.04 (0.71–1.42); *p*: 0.84 1.11 (0.85–1.45); *p*: 0.44
Blevins AM, et al. R, SC, [33]	2019	USA	Adult patients with or without	KDIGO	100	2492	76.0 vs. 82.7 vs. 78.0	12.0 vs. 12.0 vs. 11.6	4.0 vs. 3.0 vs. 3.0	TZP–VAN vs. MER–VAN vs. FEP–VAN	39.3% vs. 23.5% vs.

Considering the absence of randomized controlled trials comparing the risk of AKI with TZP–VAN and FEP–VAN or MER–VAN, meta-analyses evaluating the same pool of observational studies may only serve to amplify bias. Nevertheless, seven meta-analyses have been reported to address the relationship between TZP–VAN and AKI [5][12][13][42][43][44][45]. Hammond et al. conducted a meta-analysis that included 14 observational studies and showed that TZP–VAN was significantly associated with a higher rate of AKI compared to FEP–VAN or MER–VAN in adults (the adjusted odds ratio (OR, 3.15; 95% CI, 1.72–5.76) [13]. However, it is noteworthy that substantial statistical heterogeneity was found among the studies (I^2 = 78.1%). In another meta-analysis, Giuliano et al. evaluated 15 observational studies, 7 of which overlapped with the studies included in the meta-analysis by Hammond et al. [5]. The authors demonstrated considerable risk for AKI with TZP–VAN compared to vancomycin with or without another β-lactam (OR, 3.649; 95% CI, 2.157–6.174; I^2 = 83.5%; $p < 0.001$) [5]. Furthermore, this association remained significant when the TZP–VAN combination was compared to VAN alone (OR, 3.980; 95% CI, 2.749–5.763; I^2 = 31.4%; $p < 0.001$). In a recent meta-analysis (47 cohort studies with a total of 56,984 adult and pediatric

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			[12] renal dysfunction								24.2%; OR, 2.16 (1.62–2.88); *p*: < 0.001
Kang S, et al. R, SC, [34]	2019	South Korea	Adult patients with or without renal dysfunction	KDIGO	100	340	Yes, percentage unknown	Not provided	6.5 vs. 8.0 vs. 8.0	TZP–VAN vs. MER–VAN vs. VAN	52.7% vs. 27.7% vs. 25.7%; *p*: <0.001
Molina KC, et al. R, SC, [35]	2019	USA	Adult patients without renal dysfunction	AKIN	100	394	Yes, percentage unknown	11.2 vs. 11.0	3.3 vs. 3.7	TZP–VAN vs. FEP–VAN	28.7% vs. 21.3%; OR, 1.50 (0.88–2.57); *p*: 0.13
Haruki Y, et al. R, SC, [36]	2020	Japan	Adult patients without renal dysfunction	RIFLE	25.0 vs. 28.3	272 [46]	68.5 vs. 67.8	13.3 vs. 13.4	6.0 vs. 7.0	TZP–VAN vs. VAN-Other β-lactams	25.0% vs. 12.2%; OR, 2.40 (1.20–4.78); *p*: 0.01
O' Callaghan K et al. R, SC, [37]	2020	Australia	Adult patients with or without renal dysfunction [12][21]	AKIN	100	260	Yes, percentage unknown	Not provided	4.0 vs. 5.0	TZP–VAN vs. MER–VAN or FEP–VAN	RRR, 2.2 (1.0–4.9); *p*: 0.05
Yabes JM, et al. R, SC, [38] [47][48]	2021	USA	Adult patients without renal dysfunction	RIFLE and AKIN	88.5 vs. 93.7	268	Yes, percentage unknown	9.4 vs. 10.9	Not provided	TZP–VAN vs. VAN-Other β-lactams	13.1% vs. 9.7%; OR, 1.72 (1.02–2.76); *p*: 0.04
Aslan AT, et al. R, SC, [39]	2021	Turkey	Adult patients with or without	RIFLE	32.0 vs. 34.6	154	Yes, percentage unknown	Not provided	5.0 vs. 9.0	TZP–VAN vs. MER–VAN	40.0% vs. 24.0%; aOR,

3. Epidemiology of TZP Plus VAN-Associated AKI in ICU Patients

Although many observational studies have included ICU patients as part of the entire cohort, eight studies have investigated the risk of AKI only in ICU patients receiving TZP–VAN compared to patients receiving FEP–VAN or those receiving FEP–VAN or MER–VAN. All these studies have retrospective single-center designs with sample sizes ranging from 122 to 3299. Except for two studies (one from South Korea and the other from Australia), all were published in the USA. Among them, Blevins et al. reported that the AKI rates were 39.3% for TZP–VAN patients, 24.2% for FEP–VAN patients, and 23.5% for MER–VAN patients ($p < 0.0001$ for both comparisons). Similarly, the frequencies of stage II and stage III AKI were also significantly higher for TZP–VAN patients than for other patients receiving MER–VAN or FEP–VAN (15% and 6.6% for TZP–VAN patients, 5.8% and 1.8% for FEP–VAN patients, and 6.6% and 1.3% for MER–VAN patients, $p < 0.0001$ for both comparisons). In a multivariate

Authors and Type	Year	Country	Population	Definition of AKI *	ICU Residence and/or Critically Ill, %	Sample Size, *n*	Exposure to Other Nephrotoxins, %	Mean or Initial VAN Trough Level (mg/dl)	Treatment Duration, Days	Comparison Groups	Rate of AKI
[33]			renal dysfunction				[20][30][32][35][37][41]		[34]		2.28 (1.01–5.18); *p*: 0.048
Tookhi RF, et al. R, SC, [40]	2021	Saudi Arabia	Adult patients without renal dysfunction [13]	KDIGO	18.2 vs. 30.9	158	49.4 vs. 51.9	Not provided	Not provided	TZP–VAN vs. MER–VAN	10.4% vs. 21.0%; *p*: 0.07
Elliott BP, et al. R, SC, [41]	2022	USA	Adult patients with sepsis	KDIGO	100	418	Yes, percentage unknown [43]	Not provided	Not provided	TZP–VAN vs. FEP–VAN	15.2% vs. 11.0%; *p*: 0.44

62–2.88) mparison although ly, these ammond ≥50% of R, 2.83; atients (n –VAN or comitant

administration of TZP and VAN had the highest probability of AKI as compared to other groups in a separate analysis of ICU patients (i.e., VAN monotherapy, FEP–VAN, and MER–VAN). However, the results did not reach statistical significance when compared with other combinations [12]. It is unclear why a statistically significant difference in AKI risk could not be obtained in ICU patients in those receiving TZP–VAN compared to other comparison groups. Nevertheless, some specific risk factors prevailingly seen in ICU patients, such as critical illness, hypotension, and exposure to vasopressors, may have precluded researchers to uncover the real impact of TZP–VAN exposure on the risk of AKI. More data are needed to clarify the precise pathophysiological mechanism(s) for the reasons of the non-significant association between TZP–VAN exposure and AKI compared to VAN plus FEP or MER in ICU patients.

Abbreviations: R, retrospective; SC, single-center; P, prospective; MC, multicenter; AKI, acute kidney injury; n number; ICU, intensive care unit; VAN, vancomycin; TZP, piperacillin-tazobactam; FEP, cefepime; MER, meropenem; OR, odds ratio; aOR, adjusted odds ratio; HR, hazard ration; aHR, adjusted hazard ratio; RRR, relative risk reduction. * For definitions of AKI, please see text.

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