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Is There a Difference in Acute Kidney Injury Incidence Among Patients Treated with Piperacillin-Tazobactam or Levofloxacin?

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Abstract

Background: Recent literature supports increased acute kidney injury (AKI) in patients treated with piperacillin-tazobactam (PTZ) and vancomycin (VAN); however, these studies utilize alternative ß-lactam as the comparator group, which may be flawed due to underlying nephrotoxic potential of these agents. This study sought to determine if there was a difference in AKI rate in patients treated with PTZ and levofloxacin (LEV).

Methods: This retrospective cohort study examined adult patients admitted between 1/1/2010 and 12/31/2014, who received at least 2 days of PTZ or LEV. Demographic and clinical data were collected from the University of Kentucky Center for Clinical and Translational Science Enterprise Data Trust. AKI was assessed using the RIFLE criteria. Patients were matched on baseline creatinine clearance, receipt of other nephrotoxic agents, and comorbidities that predispose to AKI. Patients receiving VAN in the LEV arm were exactly matched to patients receiving VAN in the PTZ arm.

Results: Overall, 3,672 patients were included for analysis (2,538 PTZ and 1,134 LEV). The average age was 52±17 years, 52% of patients were male, and median Charlson score was 4 (2-8). AKI incidence was higher in the PTZ group (24.6% v 12.6%, p<0.0001), with higher rates in each stratification of the RIFLE criteria. Baseline characteristics that were still different following matching were gender, race, Charlson comorbidity index, baseline creatinine clearance, hypertension, heart failure, and exposure to ACE inhibitors or contrast. The PTZ group had higher AKI rates in the matched cohort (19.7% vs 13.1%, p=0.0002). Controlling for confounding variables, the PTZ group had an adjusted OR of 1.63 (1.26-2.10) when compared to the LEV group. When taking into account VAN exposure, PTZ+VAN patients were more likely to experience AKI than those receiving LEV+VAN (30.6% v 16.9%, p=0.0004, aOR 2.17 [1.43-3.35]). Similarly, patients receiving PTZ alone were more likely to have an AKI compared to LEV alone (15.6% v 11.7%, p=0.04, aOR 1.39 [1.02-1.92]).

Conclusions: In this comparator-controlled study, PTZ was associated with higher AKI rates than LEV. Additionally, the increase in AKI incidence when VAN was added to PTZ was greater than when VAN was added to LEV.

Background

- Piperacillin-tazobactam (PTZ) has recently been implicated in higher rates of acute kidney injury (AKI) when compared to other β-lactam agents
- Levofloxacin (LEV), a fluoroquinolone antibiotic, is generally consider non-nephrotoxic and has similar indications as PTZ

Objective

- Determine if there is a difference in AKI in patients treated with PTZ or LEV

Results

Table 1: Patient characteristics in unmatched and matched cohorts

Variable	Unmatched			Matched		
	LEV (N=1,134)	PTZ (N=2,538)	p	LEV (N=929)	PTZ (N=929)	p
Age (median [IQR])	56 (45-67)	52 (39-63)	**<0.00001**	56 (45-67)	55 (44-65)	0.08
Male gender	478 (42.2%)	1,468 (57.8%)	**<0.00001**	390 (42.0%)	463 (49.8%)	**0.0008**
Caucasian	1,007 (88.8%)	2,330 (91.8%)	**0.004**	826 (88.9%)	858 (92.4%)	**0.01**
Weight (median [IQR])	75.3 (62.6-92)	77.1 (63.0-93.0)	0.3	75.3 (62.1-92.3)	77.1 (63.1-90.7)	0.6
BMI (median [IQR])	26.3 (22.0-32.0)	26.3 (21.8-31.5)	0.5	26.2 (21.8-32.0)	26.6 (22.0-31.9)	0.8
CCI (median [IQR])	5 (3-8)	3 (2-7)	**<0.00001**	5 (3-8)	4 (2-8)	**<0.00001**
Hypotension	541 (47.7%)	1,331 (52.4%)	**0.009**	447 (48.1%)	468 (50.4%)	0.4
Baseline CrCl (median [IQR])	85.1 (60.1-116.1)	97.6 (67.5-131.6)	**<0.00001**	82.7 (59.1-113.3)	92.3 (64.0-126.2)	**0.0002**
Baseline CrCl group			**<0.00001**			**0.0004**
30-59 mL/min	281 (24.8%)	483 (19.0%)		241 (26.0%)	200 (21.5%)	
60-89 mL/min	338 (29.8%)	628 (24.7%)		287 (30.9%)	243 (26.2%)	
≥90 mL/min	515 (45.4%)	1,427 (56.2%)		401 (43.2%)	486 (52.3%)	
Concomitant nephrotoxins						
Aminoglycoside	38 (3.4%)	408 (16.1%)	**<0.00001**	38 (4.1%)	36 (3.9%)	0.9
Amphotericin B	4 (0.4%)	22 (0.9%)	0.1	4 (0.4%)	4 (0.4%)	1
ACE inhibitor	284 (25.0%)	404 (15.9%)	**<0.00001**	234 (25.2%)	168 (18.1%)	**0.0003**
Contrast	33 (2.9%)	142 (5.6%)	**0.0006**	30 (3.2%)	59 (6.4%)	**0.002**
Loop diuretic	360 (31.8%)	817 (32.2%)	0.8	301 (32.4%)	269 (29.0%)	0.1
NSAID	159 (14.0%)	422 (16.6%)	0.05	134 (14.4%)	153 (16.5%)	0.2
Calcineurin inhibitor	88 (7.8%)	197 (7.8%)	1	78 (8.4%)	79 (8.5%)	1
Vancomycin	256 (22.6%)	1,720 (67.8%)	**<0.00001**	255 (27.5%)	255 (27.5%)	1
Vasopressor	44 (3.9%)	201 (7.9%)	**<0.00001**	42 (4.5%)	45 (4.8%)	0.8
Comorbidities						
Diabetes	332 (29.3%)	711 (28.0%)	0.5	272 (29.3%)	263 (28.3%)	0.7
Heart Failure	185 (16.3%)	281 (11.1%)	**<0.00001**	160 (17.2%)	108 (11.6%)	**0.0008**
Hypertension	657 (57.9%)	1,271 (50.1%)	**<0.00001**	541 (58.2%)	473 (50.9%)	**0.002**
Cystic Fibrosis	29 (2.6%)	193 (7.6%)	**<0.00001**	28 (3.0%)	28 (3.0%)	1

Figure 1: Unadjusted AKI incidence in PTZ and LEV patients

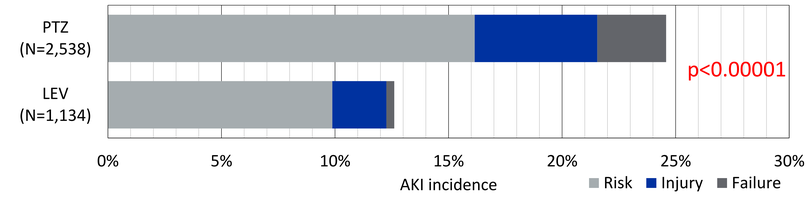

Figure 2: AKI incidence in matched cohort

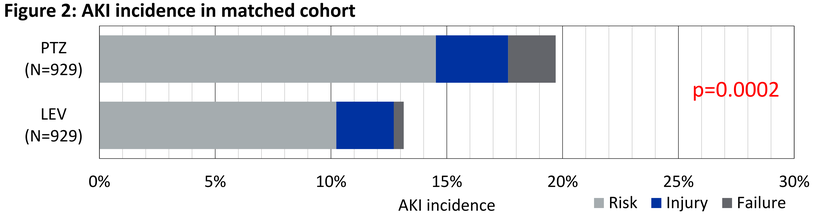

Figure 3: Impact of concomitant VAN therapy on AKI incidence in matched cohort

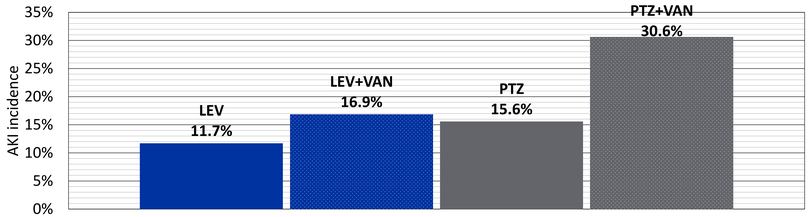

Table 2: Multivariate regression results in matched cohort stratified by VAN exposure

Covariate	OR	95%CI	p
Treatment			
LEV	(ref)		
LEV+VAN	1.50	1.00-2.25	**0.049**
PTZ	1.39	1.02-1.92	**0.040**
PTZ+VAN	3.27	2.28-4.70	**<0.0001**
ACE inhibitor	1.46	1.08-1.96	**0.012**
CCI (per point increase)	1.03	1.00-1.06	0.089
Baseline CrCl (mL/min)			
30-59	(ref)		
60-89	0.82	0.56-1.20	0.30
≥ 90	1.57	1.14-2.19	**0.0063**

Methods

- Clinical data were collected from the UK Center for Clinical and Translational Science Enterprise Data Trust from 1/1/2010 through 12/31/2014
- Adult patients were included if they received PTZ or LEV for ≥48 hours
- Patients were excluded for: pregnancy, chronic kidney disease, baseline creatinine clearance (CrCl)<30 mL/min, receipt of CFP or MEM
- CrCl was calculated with the adjusted Cockcroft-Gault equation
- Exposure to nephrotoxic drugs was defined as receiving at least 1 dose of the agent within 24 hours of treatment initiation through discontinuation
- Comorbidities were identified with ICD-9 codes
- Hypotension was defined as MAP<65 mmHg, SBP<90 mmHg, or vasopressor exposure during treatment
- Charlson Comorbidity index (CCI) was used to measure severity of illness
- AKI was defined as meeting any of the RIFLE criteria
- Patients were matched on: CrCl, comorbidities, and nephrotoxic drug exposures
- Patients were matched exactly on vancomycin (VAN) exposure
- Univariate and multivariate logistic regressions were performed

Conclusions

- PTZ was associated with higher AKI rates than LEV
- AKI incidence increased for both groups when VAN is added to either agent
- The magnitude of increase was larger in the PTZ-VAN group compared to the LEV-VAN group when compared to PTZ or LEV, respectively.

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