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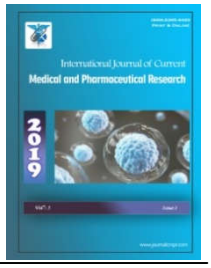

THE RISK OF ANTIBIOTICS ASSOCIATED HYPERNATRAEMIA AMONG SEPTIC CRITICALLY ILL PATIENTS WHO ARE TAKING EMPIRICAL OR TARGETED BROAD SPECTRUM BETA-LACTAM ANTIBIOTICS

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ABSTRACT

Objectives: Antibiotic associated hypernatremia (AAH) is a frequent concern in critically ill patients who are taking β-lactam antibiotics (ABs) especially Piperacillin/Tazobactam. The consequences of AAH may have detrimental effects on critically ill patients. The objective of this study is to evaluate the AAH risk of the most commonly used broad spectrum β-lactam ABs.

Methods: We performed a retrospective analysis of patients admitted to the adult intensive care unit (ICU) between April 2017 and Sep 2018 who were their demographics, fluid inputs and outputs, antibiotics dose and duration, and corrected sodium can be obtained. Collected data were analyzed by one-way ANOVA test followed by Tukey Kramer Post Hoc test to determine the mean differences of significant dependent variables between the Meropenem (Group I), Imipenem/Cilastatin (Group II), Piperacillin/Tazobactam (Group III), and Cefepime (Group IV). Also, gender and risk of AAH were analyzed by chi square test.

Results: The mean overall age was 58.37±0.78 years, and 112 subjects (68.71%) were male. The overall risk of AAH was 12.3%. Group III patients had the highest risk of AAH (36.4%) followed by Group I (7.9%), Group II (2.4%), and finally Group IV (0.00%). The mean difference of corrected average sodium levels (cNa^{+}_{avg}) was significantly highest between Group III and IV (3.30±0.21) followed by Group I and IV (1.82±0.22) and finally between Group I and II (1.42±0.21).

Conclusion: Our results demonstrate that empirical or targeted use of β-lactam ABs is an independent risk of AAH especially in case of high dose of Piperacillin/Tazobactam and Meropenem.

INTRODUCTION

Hypernatremia is not common among non ICU hospitalized patients with a prevalence of 0.2% upon admission and 1% during admission [1]. In contrast, hypernatremia is more common in critically ill patients with a prevalence of 4% ± 2% upon admission [2-3] and 7% ± 3% for surgical ICU patients or 16% ± 10% for medical ICU patients attributed to theadministration of hypertonic solutions, resuscitation crystalloids, irrigation solutions, enteral and parenteral feeding, maintenance crystalloids fluids, and administration of sodium-rich antibiotics [4-10].AAH is a frequent concern in critically ill patients who are taking β-lactam ABs especially Piperacillin/Tazobactam. The consequences of AAH may have detrimental effects on critically ill patient's organ functions and may be an independent risk factor for mortality. The objective of this study is to evaluate the AAH risk of the most commonly used broad spectrum β-lactam ABs.

METHODS

Study design and setting

We conducted a single-center observational retrospective study in the department of adult ICU of King Hussein Medical Center (KHMC) at Royal Medical Services (RMS) in Jordan to assess the risk of AAH of four commonly used broad spectrum β-lactam ABs in empirical management for at least 2 days as described in Table 1. This study was approved by our Institutional Review Board (IRB), and a requirement for consent was waived owing to its retrospective design. This study included a cohort of critically ill patients admitted to our adult ICU via the emergency department (ED) or via other hospital wards with any medical or surgical problem. Flow chart of critically ill patient's selection and data collectionprocess is fully illustrated in Figure 1.

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Table 1 Studied critically ill patients group's description

Group #	Group I	Group II	Group III	Group IV
Description	Critically ill patients who were on Meropenem (Meronem®)	Critically ill patients who were on Imipenem/Cilastatin (Tienam®)	Critically ill patients who were on Piperacillin/Tazobactam (Tazocin®)	Critically ill patients who were on Cefepime (Maxipim®)

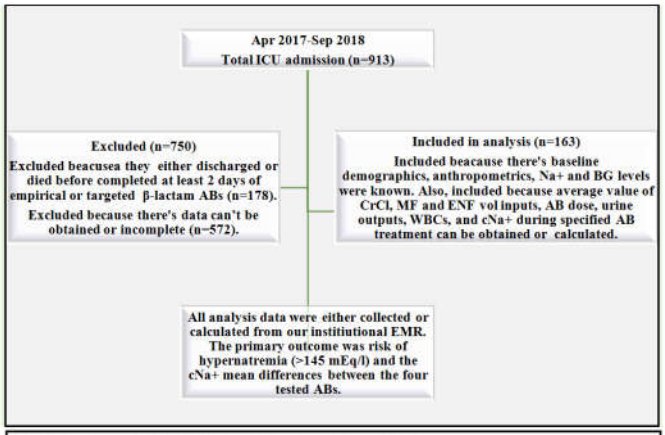

Fig 1. Flow chart of critically ill patient's selection and data collection process.

Apr: April. ABs: Antibiotics. CrCl: Creatinine clearance.
Sep: September. Na+: Sodium. MF: Maintenance fluid.
ICU: Intensive Care Unit. BG: Blood glucose. ENF: Enteral nutritional formula.

Statistical analysis

The collected data of each desired outcome in Group I-IV were analyzed using one-way ANOVA test to compare the mean value of dependent variables among groups followed by Tukey Kramer Post Hoc testto determine the mean differences of significant dependent variables betweeneach group of the four tested groups. In case of gender (male or female) and risk of AAH were presented as number (percentage) using chi square analysis. Statisticalanalyses were performed using IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA) and P-values ≤0.05 were considered statistically significant.

RESULTS

Characteristics of the subjects

The mean overall age was 58.37±0.78 years, and 112 subjects (68.71%) were male. The overall risk of AAH was 12.3% (20 patients). Critically ill patients who were on Piperacillin/Tazobactam had the highest risk of AAH (36.4%) followed by Meropenem (7.9%), Imipenem/Cilastatin (2.4%), and finally Cefepime with no risk of AAH. The mean difference of corrected average sodium levels (cNa^+_{avg}) was significantly highest between Group III and IV (3.30±0.21 mEq/l) followed by Group I and IV (1.82±0.22 mEq/l) and finally between Group I and II (1.42±0.21 mEq/l).Demographics, anthropometrics, and follow-up comparison data of the study's critically ill patients are fully summarized in Table 2 and Table 3.

DISCUSSION

The present study included septic mechanically ventilated critically ill patients who were taking either empirical or targeted β-lactam ABs for at least 2 days at overall duration of 7.40±0.27 days. Because the major sources of Na^+ inputs in this study were maintenance fluid (MF), enteral nutritional formula (ENF), human albumin (H.ALB), and broad spectrum β-lactam ABs and there were insignificant differences between the four groups regarding average MFs, ENFs, and H.ALB, the significant changes in Na^+ during antibiotics administration were likely from β-lactam ABs. Meropenem has the highest Na^+ load of the four tested β-lactam ABs (3.92 mEq Na^+/g AB) followed by Imipenem/Cilastatin (3.2 mEq Na^+/g AB) and Piperacillin/Tazobactam (2.51 mEq Na^+/g AB) and finally Cefepime with zero mEq Na^+ load due to its hydrochloride salt.

Table 2 Demographics, anthropometrics, and follow-up dependent variable data of the four tested groups.

Dependent Variable	Group I N=38 Mean±SEM	Group II N=42 Mean±SEM	Group III N=44 Mean±SEM	Group IV N=39 Mean±SEM	Total N=163 Mean±SEM	*P*-Value
Age (Yrs)	57.79±1.46	61.45±1.73	58.50±1.33	55.46±1.61	58.37±0.78	0.056 (NS)
Gender **Male**	27 (71.1%)	30 (71.4%)	33 (75.0%)	22 (56.4%)	112 (68.7%)	0.284 (NS)
Gender **Female**	11 (28.9%)	12 (28.6%)	11 (25.0%)	17 (43.6%)	51 (31.3%)	
BW_0 (Kg)	78.16±1.70	74.21±1.44	69.86±1.56	75.08±1.49	74.17±0.80	0.003(S)
BMI_0 (Kg/m^2)	28.04±0.52	26.02±0.59	23.51±0.57	26.47±0.61	25.92±0.31	0.000(S)
Na^+_0 (mEq/l)	138.08±0.17	137.97±0.12	138.14±0.12	138.29±0.14	138.12±0.07	0.404(NS)
BG_0 (mg/dl)	148.50±1.43	176.14±1.29	175.98±1.20	156.69±3.57	165.00±1.39	0.000(S)
c Na^+_0 (mEq/l)	138.85±0.17	139.19±0.12	139.36±0.11	139.21±0.16	139.16±0.07	0.090(NS)
$WBCs_{avg}$ (Cells/µl)	11152±1851	9883±1254	11391±1190	12502±1433	11212±712	0.640(NS)
$CrCl_{avg}$ (ml/min)	51.07±7.58	55.06±7.52	38.13±2.94	49.89±9.09	48.32±3.50	0.332(NS)
Urine $Output_{avg}$ (ml/d)	865.5±73.1	884.9±73.2	703.0±29.9	841.5±87.9	820.9±34.1	0.203(NS)
AB $Dose_{avg}$ (mg/d)	4158±263	1976±117	10636±396	3462±265	5178±303	0.000(S)
AB $Duration_{avg}$ (Days)	7.55±0.58	7.26±0.49	7.80±0.55	6.97±0.58	7.40±0.27	0.732(NS)
AB Na+ $Input_{avg}$ (mEq/d)	16.29±1.03	6.32±0.37	26.71±0.99	0.00±0.000	12.64±0.89	0.000(S)
MF vol_{avg} (ml/d)	2904±8	2899±6	2907±6	2915±7	2906±3	0.405(NS)
MF Na+ $Input_{avg}$ (mEq/d)	223.59±0.66	223.19±0.47	223.84±0.45	224.45±0.55	223.76±0.27	0.406(NS)
ENF Vol_{avg} (ml/d)	407.6±15.5	403.1±15.1	440.8±6.9	419.2±14.6	418.2±6.7	0.171(NS)
ENF Na+ $Input_{avg}$ (mEq/d)	14.88±0.57	14.71±0.55	16.09±0.25	15.29±0.53	15.26±0.24	0.171(NS)
Na^+_{avg} (mEq/l)	142.63±0.17	141.23±0.12	144.08±0.12	140.83±0.18	142.23±0.13	0.000(S)
BG_{avg} (mg/dl)	162.97±3.25	162.43±1.81	172.07±2.12	161.31±3.13	164.89±1.33	0.011(S)
c Na^+_{avg} (mEq/l)	143.31±0.17	141.89±0.12	144.79±0.13	141.48±0.18	142.90±0.13	0.000(S)
Risk of AAH Positive (>145 mEq/l)	3 (7.9%)	1 (2.4%)	16 (36.4%)	0 (0.0%)	20 (12.3%)	0.000(S)
Risk of AAH Negative (≤145 mEq/l)	35 (92.1%)	41 (97.6%)	28 (63.6%)	39 (100.0%)	143 (87.7%)	
ALB $level_{avg}$ (g/dl)	2.63±0.02	2.66±0.02	2.61±0.02	2.56±0.02	2.61±0.01	0.006(S)
H.ALB infused avg (g/d)	19.47±0.37	19.52±0.33	19.77±0.23	20.00±0.00	19.69±0.14	0.510(NS)

Data are presented as Mean±Standard error of mean and are analyzed by using ANOVA test (at p-value< 0.05).

- ❖S: Significant.
- ❖NS: Non-significant.
- ❖Group I: Critically ill patients who were on Meropenem.
- ❖Group II: Critically ill patients who were on Tienam®.
- ❖Group III: Critically ill patients who were on Tazocin®.
- ❖Group IV: Critically ill patients who were on Cefepime.
- ❖IBW: Ideal body weight.
- ❖BW: Body weight.
- ❖BMI: Body mass index.
- ❖BG: Blood glucose.
- ❖AB: Specified antibiotic.
- ❖MF: Maintenance fluid.
- ❖AAH: Antibiotic associated hypernatremia.
- ❖H.ALB: Human albumin 20% IV.
- ❖Na^+: Sodium.
- ❖cNa^+: Corrected sodium.
- ❖ALB: Albumin.
- ❖avg: Average during antibiotic administration.
- ❖0: Baseline dependent variable before intervention.
- ❖ENF: Enteral nutritional formula (Ensure® in this study).
- ❖CrCl: Creatinine clearance.
- ❖WBCs: White blood cells.

Table 3 Multiple comparison of the significant dependent variables between the four tested groups

Dependent Variable	Group I vs II Mean diff±SEM (Sig)	Group I vs III Mean diff±SEM (Sig)	Group I vs IV Mean diff±SEM (Sig)	Group II vs III Mean diff±SEM (Sig)	Group II vs IV Mean diff±SEM (Sig)	Group III vs IV Mean diff±SEM (Sig)
BW_0 (Kg)	3.94±2.21 (NS)	8.29±2.19 (S)	3.08±2.25 (NS)	4.35±2.13 (NS)	-0.86±2.19 (NS)	-5.21±2.17 (NS)
BMI_0 (Kg/m^2)	2.02±0.82 (NS)	4.53±*0.81 (S)	1.57±0.84 (NS)	2.52±0.79 (S)	-0.45±0.82 (NS)	-2.96±0.81 (S)
BG_0 (mg/dl)	-27.64±2.94 (S)	-27.48±2.90 (S)	-8.19±2.99 (S)	0.17±2.83 (NS)	19.45±2.92 (S)	19.29±2.88 (S)
AB Dose $_{avg}$ (mg/d)	21812±405 (S)	-6478±401 (S)	696±413 (NS)	-8660±391 (S)	-1485±403 (S)	7175±398 (S)
AB Na+ Input $_{avg}$ (mEq/d)	9.98±1.07 (S)	-10.41±1.05 (S)	16.29±1.09 (S)	-20.39±1.03 (S)	6.32±1.06 (S)	26.71±1.05 (S)
Na^+_{avg} (mEq/l)	1.39±0.21 (S)	-1.45±0.21 (S)	1.79±0.21 (S)	-2.85±0.20 (S)	0.39±0.21 (NS)	3.25±0.21 (S)
BG_{avg} (mg/dl)	0.55±3.70 (NS)	-9.09±3.66 (NS)	1.67±3.77 (NS)	-9.64±3.57 (S)	1.12±3.68 (NS)	10.76±3.64 (S)
c Na^+_{avg} (mEq/l)	1.42±0.21 (S)	-1.48±0.21 (S)	1.82±0.22 (S)	-2.89±0.21 (S)	0.40±0.21 (NS)	3.30±0.21 (S)
ALB level $_{avg}$ (g/dl)	-0.02±0.03 (NS)	0.03±0.03 (NS)	0.08±0.03 (NS)	0.05±0.03 (NS)	0.09±0.03 (S)	0.05±0.03 (NS)

Data are presented as Mean difference ±Standard error of mean and are analyzed by using Tukey Kramer post-hoc multiple comparison analysis (at p-value< 0.05).

- ❖S: Significant.
- ❖NS: Non-significant.
- ❖Group I: Critically ill patients who were administered Meropenem.
- ❖Group II: Critically ill patients who were administered Imipenem/Cilastatin.
- ❖Group III: Critically ill patients who were administered Piperacillin/Tazobactam.
- ❖Group IV: Critically ill patients who were administered Cefepime.
- ❖cm: Centimeter.
- ❖Kg: Kilogram.
- ❖IBW: Ideal body weight.
- ❖BW: Body weight.
- ❖BMI: Body mass index.
- ❖BG: Blood glucose.
- ❖AB: Specified antibiotic.
- ❖d:Day.
- ❖mg: Milligram.
- ❖Na^+: Sodium.
- ❖cNa^+: Corrected sodium.
- ❖ALB: Albumin.
- ❖mEq: Millequivalent.
- ❖0: Baseline dependent variable before intervention.
- ❖avg: Average of dependent variable during antibiotic administration.

In our study we showed that the greatest impact of AAH was in Piperacillin/Tazobactam patients group (Group III) followed by Meropenem patients group (Group I) and Imipenem/Cilastatin patients group (Group II). These contrary results can be explained by the high variability of AB renal adjusted dose inputs, which was significantly highest in Group III (10636±396 mg AB/day) followed by Group I (4158±263 mg AB/day) and Group II (1976±117 mg AB/day). To calculate AB Na^+ input (mEq Na^+/day), we multiplied AB Na^+ load (mEq Na^+ /g AB) by AB dose input (g AB/day). The AB Na^+ input in our study was significantly higher in Group III (26.71±0.99 mEq Na^+/day) followed by Group I (16.29±1.03 mEq Na^+/day) and Group II (6.32±0.37 mEq Na^+/day). In summary, our results demonstrate that empirical or targeted use of β-lactam ABs is an independent risk of AAH especially in case of high dose of Piperacillin/Tazobactam and Meropenem. This study is limited by its retrospective design, using single-center data, including only septic ICU patients. Nonetheless, our center is an experienced and high-volume unit, so our data may be useful in other centers. A larger, multisite, and prospective study is needed to control for multiple confounders

References

1. Palevsky PM, Bhagrath R, Greenberg A. Hypernatremia in hospitalizedpatients. Ann Intern Med 1996;124:197-203.
2. Lindner G, Funk GC, Schwarz C, *et al*. Hypernatremia in the criticallyill is an independent risk factor for mortality. Am J Kidney Dis 2007;50:952-7.
3. Funk GC, Lindner G, Druml W, *et al*. Incidence and prognosis ofdysnatremias present on ICU admission. Intensive Care Med 2010;36:304-11.
4. Darmon M, Timsit JF, Francais A, *et al*. Association betweenhypernatraemia acquired in the ICU and mortality: a cohort study. Nephrol Dial Transplant 2010;25:2510-5.
5. Lindner G, Funk GC, Lassnigg A, *et al*. Intensive care-acquiredhypernatremia after major cardiothoracic surgery is associated with increased mortality. Intensive Care Med 2010;36:1718-
6. Stelfox HT, Ahmed SB, Khandwala F, *et al*. The epidemiology of intensive care unit-acquired hyponatraemia and hypernatraemia inmedical-surgical intensive care units. Crit Care 2008; 12:R162.

7. Stelfox HT, Ahmed SB, Zygun D, *et al*. Characterization of intensivecare unit acquired hyponatremia and hypernatremia following cardiacsurgery. Can J Anaesth 2010;57:650-8
8. O'Donoghue SD, Dulhunty JM, Bandeshe HK, *et al*. Acquiredhypernatraemia is an independent predictor of mortality in critically illpatients. Anaesthesia 2009;64:514-20.
9. Polderman KH, Schreuder WO, Strack van Schijndel RJ *et al*. Hypernatremia in the intensive care unit: an indicator of quality of care? Crit Care Med 1999; 27: 1105–1108
10. Hoorn EJ, Betjes MG, Weigel J *et al*. Hypernatraemia in critically ill patients: too little water and too much salt. Nephrol Dial Transplant 2008; 23: 1562–1568.

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