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국내 3차 병원의 비만 암환자에서 각각 다른 체중 측정 공식들을 적용한 piperacillin/tazobactam의 용량 적절성 비교 연구

김지현[1#]·양영모[2#]·윤현옥[3]·최은주[2*]

[1]화순전남대학교병원, [2]조선대학교 약학대학, [3]경상대학교 약학대학
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Comparison of Appropriate Piperacillin/Tazobactam Doses in Korean Obese Patients with Cancer Based on Different Body Size Descriptor Equations in a Tertiary Care Hospital

Ji Hyun Kim[1#], Young-Mo Yang[2#], Hyonok Yoon[3], and Eun Joo Choi[2,*]

[1]Department of Pharmacy, Chonnam National University, Hwasun 58128, Hospital, Hwasun, Republic of Korea
[2]College of Pharmacy, Chosun University, Gwangju 61452, Republic of Korea
[3]College of Pharmacy, Research Institute of Pharmaceutical Science, Gyeongsang National University, Gyeongnam 52828, Republic of Korea
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ABSTRACT

Background: Piperacillin/tazobactam (TZP) is an antibiotic against a broad spectrum of gram–positive, gram–negative, and aerobic and anaerobic strains of bacteria. Due to changes in its pharmacokinetic and pharmacodynamic parameters by TZP–treated patients' renal functions and obesity, it is important to administrate and monitor TZP based on their renal functions and Body Mass Index (BMI) levels. The purpose of this study was to determine the appropriateness of administration doses of TZP based on renal functions of obese cancer patients in a tertiary hospital. **Methods:** This study was retrospectively conducted with obese cancer patients with BMI ≥ 30 kg/m2 in a tertiary hospital, Korea from September 2004 to August 2014. Data were collected through Electronic Medical Record (EMR) which contained laboratory data and TZP dosing of each patient. **Results:** Among 7,058 patients during the study period, 102 prescriptions were selected based on inclusion and exclusion criteria and classified by their renal functions. Although TZP should be used based on patients' renal functions to adjust its dose, its initial dose and dosing interval were consistently used without considering patients' renal functions on a regular basis. Especially, in the comparison with FDA dosing standard of TZP, approximately twice patients with 20 mL/min ≤ CrCl ≤ 40 mL/min received domestically 4.5 g instead of 2.25 g as the TZP starting dose. **Conclusion:** The appropriate doses of TZP were administered to almost all of obese cancer patients; however, the recommended TZP dose was different between Korea and other countries by twice the amount. Further related studies are necessary to clearly determine the results, to optimize TZP treatment for obese patients with cancer in clinical practice, and to design and develop new TZP formulations for them in pharmaceutical industry.

KEY WORDS: Piperacillin/tazobactam, dose appropriateness, obese cancer patients

Piperacillin/tazobactam (TZP) is a broad-spectrum antibiotic with coverage against gram-positive, gram-negative, and aerobic/anaerobic organisms, and is used principally to treat pneumonia, peritonitis, febrile neutropenia, and intra-abdominal infection, as well as for prophylactic treatment.[1-3] TZP has reliable activity against *Pseudomonas aeruginosa*, which is resistant to multiple antibiotics; therefore, it plays an important role in treating patients with serious infections and preventing the development of resistant organisms.[4-7] According to the Infectious Diseases Society of America (IDSA) and National Comprehensive

*Correspondence to: Eun Joo Choi, College of Pharmacy, Chosun University, 309 Pilmun-daero, Dong-gu, Gwangju 61452, Republic of Korea
Tel: +82-62-230-6382, Fax: +82-62-222-5414
E-mail: ejchoi@chosun.ac.kr or pheuhot@hanmail.net
#Ji Hyun Kim and Young-Mo Yang are joint first authors and contributed equally to this work.

Cancer Network (NCCN) guidelines, TZP is recommended as an initial antibiotic to empirically treat febrile neutropenia in high-risk patients with cancer.[5,6)]

TZP elimination highly depends on renal function, and TZP excretion is interrupted if renal impairment occurs; therefore, TZP dosage should be adjusted according to the patient's renal function.[1,2,8)] In South Korea, the usual TZP dose in patients with creatinine clearance (CrCl) greater than 40 mL/min is 4.5 g intravenously (IV) every 8 hours; in patients with CrCl between 20 and 40 mL/min, the TZP dose is 4.5 g IV every 8 hours; in patients with CrCl less than 20 mL/min or hemodialysis, 4.5 g TZP is administered IV every 12 hours; in febrile neutropenic patients, 4.5 g TZP is administered IV every 6 hours with aminoglycosides.[9)] However, different renal function dependent doses of TZP are given in the USA and Canada. Specifically, the typical TZP dose in patients with CrCl greater than 40 mL/min is 3.375 g or 4.5 g IV every 6 hours depending on indications.[1)] In patients with CrCl between 20 and 40 mL/min, 2.25 g TZP is administered IV every 6 hours, and in patient with CrCl less than 20 mL/min, 2.25 g TZP is given IV every 8 hours.[1)] For patients on hemodialysis, 2.25 g TZP is administered IV every 12 hours.[1)]

The half-life of TZP is approximately 0.7-1.2 hours in patients with normal renal function; however, its half-life increases nearly two to four times in patients with CrCl less than 20 mL/min.[1,2)] Thus, it is necessary to measure accurate renal functions before TZP is administered in order to minimize TZP-induced adverse events, as well as to optimize TZP dosing. According to a study by Karino *et al*. in Japan, cautious TZP administration and monitoring was necessary in elderly patients with kidney dysfunction, particularly those with CrCl less than 40 mL/min owing to serious nephrotoxicity (although TZP is effective against hospital-acquired pneumonia).[10)]

Functional renal mass can be measured through the glomerular filtration rate (GFR) calculated from inulin injections, but this method is clinically impractical due to the time required for IV infusion and urine collection; hence, the Cockcroft-Gault (CG) equation is typically utilized to measure renal function.[11)] The pharmaceutical industry also uses the CG equation to determine renal dosage adjustments for different drugs.[12-14)] However, the use of serum creatinine concentration (SCr) as a predictive factor of kidney function in the CG equation is limited because various factors affect SCr, including age, sex, weight, and muscle mass.[11)] Specifically, SCr is linked to muscle mass, and its increase is proportionally associated with lean body weight (LBW), as opposed to total body weight (TBW).[15,16)] Consequently, weight adjustment using the CG equation is necessary to properly assess the renal function of obese patients with body mass indices (BMI) greater than or equal to 30 kg/m^2. However, the optimal weight adjustment method remains controversial.[11,15,17-21)]

To improve renal function estimation, several weight adjustment equations have been developed including ideal body weight (IBW), adjusted body weight, lean body weight published in 1976 (LBW (1976)), fat free weight, and lean body weight published in 2005 (LBW (2005)).[15,22,23)] Specifically, several researchers have demonstrated that either LBW can correct the difference between estimated GFR and absolute GFR as measured in obese patients.[15,16,19,24)] However, LBW (1976) is not likely to be useful for obese patients with TBW ≥ 125 kg or BMI ≥ 50 kg/m^2, since LBW (1976) tends to decrease in those patients, so LBW (2005) may be more appropriate for them.[15,19)] In the study conducted with morbidly obese (BMI ≥ 40 kg/m^2) patients, LBW (2005) in the CG equation provided an unbiased estimation of CrCl.[19)]

Few studies have been conducted regarding the efficacy and safety of TZP use in patients with cancer.[25,26)] However, the studies regarding appropriate TZP dosing based on renal function in patients with obesity and cancer have rarely been implemented. The objective of this study was to determine the appropriate administration dose of TZP according to the renal function of patients with obesity and cancer in a tertiary hospital.

METHODS

Study Population

Ethical approval for this study was granted by the Institutional Review Board of Chonnam National University Hwasun Hospital (CNUHH-2014-127). This study was conducted retrospectively with patients with obesity and cancer that had received TZP while hospitalized in the same hospital in South Korea between September 2004 and August 2014.

Among patients with cancer 18 years of age or older who had undergone TZP treatment for over 72 consecutive hours, those with BMI ≥ 30 kg/m^2 were included in this study, (BMI cutoff based on a review of the literature).[3,17,27-31)] If patients were re-admitted and TZP was re-administered during the study period, they were included in the study as long as they were under TZP treatment for different afflictions within that same year, or TZP was administered in a different year.[32)] However, the following exclusion criteria were applied: patients

younger than 18 years old, patients without records of height or weight essential for calculating the BMI, patients with BMI < 30 kg/m^2, patients without information regarding diagnosis and TZP administration (e.g., indication, dosage, and duration of treatment), patients without lab value information, patients who underwent TZP treatment for less than 72 hours, patients who received TZP again due to the same affliction in the same year, or patients allergic to penicillins, cephalosporins, or beta-lactamase inhibitors.[3,10,25,29,32]

Data Collection

By using electronic medical records, the following information was collected: demographics, data regarding TZP administration (e.g., indication, dosage, duration of treatment, and initial purpose of TZP use), results from bacterial identification, reasons for TZP discontinuation, antibiotics and antifungals concomitantly administered, medications that could cause drug-drug interactions with TZP, type of dialysis (if patients were under it), SCr levels just before TZP administration (in cases of TZP dose changes), and clinical and hematological values (e.g. temperature, potassium, SCr, CrCl, white blood cell, red blood cell, hemoglobin, platelet, and C-reactive protein counts) before and during TZP administration (defined as within 24 to 72 hours after TZP was initially given).[4,26,31-33]

Outcome Measures

To evaluate appropriate TZP dosing according to kidney function of obese patients with cancer, kidney function was classified into four stages by CrCl (CrCl > 40 mL/min, 20 mL/min ≤ CrCl ≤ 40 mL/min, CrCl < 20 mL/min, and hemodialysis) after a thorough literature review.[1,2,9] To calculate the CrCl values of obese patients with cancer, patient weight was calculated using three different body size descriptor equations (IBW, LBW (1976), and LBW (2005)), and those values were substituted into the CG equation to calculate CG IBW, CG LBW (1976), and CG LBW (2005).[15,16,19] After renal functions were grouped into the four predetermined stages based on the CrCl values calculated with each body size descriptor equation, the values were compared and analyzed. When SCr values < 1 mg/dL were found in patients ≥ 65 years, the values were rounded up to 1 mg/dL. When missing values for SCr occurred, the appropriate TZP dose was not assessed.

The appropriate TZP dose (one dose and total daily dose) on the 1st day of treatment, and the 2nd or 3rd day of treatment was evaluated based on the recommended TZP dose in Korea and other countries.[1,2,9] In case of hemodialysis patients, only the appropriate TZP dose on the 1st day of treatment was assessed since TZP dose was determined by whether or not patients were under hemodialysis.[1,2,9]

Statistical Analyses

SPSS 20.0 for Windows (Chicago, IL, USA) was used to analyze data. Continuous variables are presented as mean±SD, and categorical variables are presented as frequencies (n) and percentages (%). Chi-square test or Fisher's exact test was performed to examine the differences in proportions, and a one-way ANOVA was performed to compare means between groups. The level of statistical significance was set at $p<0.05$.

RESULT

Demographics

A total of 7,058 patients had taken TZP during the study period; 102 TZP prescriptions met the inclusion and exclusion criteria and were selected for the analysis (Fig. 1). Table 1 summarizes the study patients' characteristics. Thirty-eight (37.3%) prescriptions were for males, and 64 (62.7%) prescriptions were for females. The mean age of patients was 56.2 ± 16.2 years. The mean SCr before TZP administration was 1.3 ± 1.2 mg/dL. The mean BMI of the patients was 31.6

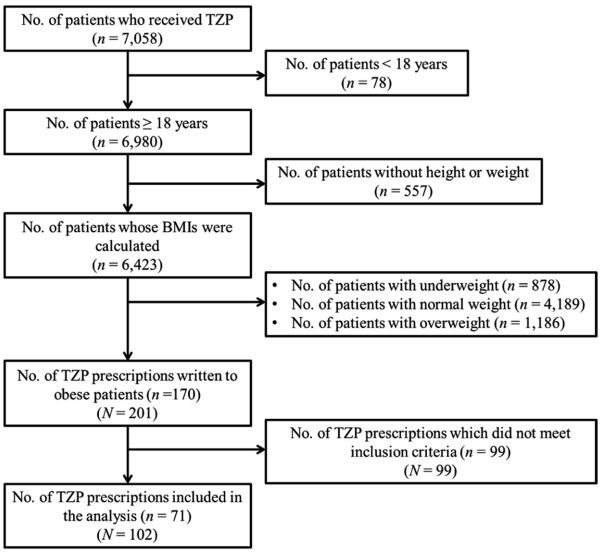

Fig. 1. Flowchart of TZP prescriptions used to assess their appropriateness for the study. The *n* indicates the number of patients, and the *N* indicates the number of TZP prescriptions. *TZP* piperacillin/tazobactam, *BMI* body mass index.

Table 1. Characteristics of the individuals who participated in the study.

Characteristic	Participants (*N* = 102)
Sex	
Male	38 (37.3)
Female	64 (62.7)
Age (years)	56.2 ± 16.2
< 30	10 (9.8)
30-39	12 (11.8)
40-49	8 (7.8)
50-59	21 (20.6)
60-69	28 (27.5)
≥ 70	23 (22.5)
Weight (kg)	81.6 ± 9.6
Height (cm)	160.5 ± 9.7
SCr (mg/dL)	1.3 ± 1.2
BMI (kg/m^2)	31.6 ± 1.5
IBW (kg)	54.5 ± 10.5
LBW (1976) (kg)	53.1 ± 10.5
LBW (2005) (kg)	50.1 ± 10.3
CrCl (mL/min)	
CG IBW	63.0 ± 38.7
CG LBW (1976)	61.2 ± 37.8
CG LBW (2005)	57.8 ± 35.9
Cancer type	
Solid cancer	55 (53.9)
Blood cancer	47 (46.1)

The analysis was performed with 102 prescriptions of piperacillin/tazobactam from 71 patients.
Values are expressed as *N* (%) for categorical variables and mean ± SD for continuous variables
SCr serum creatinine, *BMI* body mass index, *IBW* ideal body weight, *LBW (1976)* lean body weight published in 1976, *LBW (2005)* lean body weight published in 2005, *CrCl* creatinine clearance, *CG IBW* Cockcroft-Gault equation with IBW as a weight parameter, *CG LBW (1976)* Cockcroft-Gault equation with LBW (1976) as a weight parameter, *CG LBW (2005)* Cockcroft-Gault equation with LBW (2005) as a weight parameter

± 1.5 kg/m^2, and there were morbidly obese patients (BMI ≥ 40 kg/m^2) among the study subjects. The mean IBW, LBW (1976), and LBW (2005) of patients were 54.5 ± 10.5 kg, 53.1 ± 10.5 kg, and 50.1 ± 10.3 kg, respectively. The mean CG IBW, CG LBW (1976), and CG LBW (2005) of patients were 63.0 ± 38.7 mL/min, 61.2 ± 37.8 mL/min, and 57.8 ± 35.9 mL/min, respectively.

Evaluation of CrCl values based with various weight adjustment equations

Table 2 shows estimated CrCl values using CG IBW, CG LBW (1976), and CG LBW (2005). The calculated CrCl values with CG IBW were similar to those with CG LBW (1976), and slightly larger than those with CG LBW (2005). However, there were no statistically significant differences between the three groups.

Table 2. CG CrCl calculated based on various body size descriptor equations.

CrCl (mL/min)	CG IBW	CG LBW (1976)	CG LBW (2005)	*p* Value
> 40	81.9 ± 34.3	80.9 ± 33.5	78.3 ± 31.6	0.711
20-40	31.0 ± 5.1	31.2 ± 5.1	30.6 ± 5.3	0.975
< 20	18.0 ± 0.0	18.1 ± 1.4	17.6 ± 1.8	0.098
Hemodialysis	10.0 ± 4.4	10.0 ± 4.3	9.5 ± 4.4	0.993

Values are expressed as mean ± SD for continuous variables
CrCl creatinine clearance, *IBW* ideal body weight, *LBW (1976)* lean body weight published in 1976, *LBW (2005)* lean body weight published in 2005, *CG IBW* Cockcroft-Gault equation with IBW as a weight parameter, *CG LBW (1976)* Cockcroft-Gault equation with LBW (1976) as a weight parameter, *CG LBW (2005)* Cockcroft-Gault equation with LBW (2005) as a weight parameter

Appropriate initial dose of TZP based on renal functions

Table 3 presents the appropriate initial TZP dose based on various body size descriptor equations. Among 102 prescriptions, 2.25 g and 4.5 g were used as the initial TZP dose in 20 and 82

Table 3. Initial dose of TZP based on various body size descriptor equations.

CrCl (mL/min)	No. of prescriptions	2.25g, N (%)	4.5g, N (%)	*p* Value
CG IBW				
> 40	67	2 (3.0)	65 (97.0)	< 0.001
20-40	27	11 (40.7)	16 (59.3)	
< 20	2	1 (50.0)	1 (50.0)	
Hemodialysis	6	6 (100.0)	0 (0.0)	
CG LBW (1976)				
> 40	65	2 (3.1)	63 (96.9)	< 0.001
20-40	28	10 (35.7)	18 (64.3)	
< 20	3	2 (66.7)	1 (33.3)	
Hemodialysis	6	6 (100.0)	0 (0.0)	
CG LBW (2005)				
> 40	62	2 (3.2)	60 (96.8)	< 0.001
20-40	30	9 (30.0)	21 (70.0)	
< 20	4	3 (75.0)	1 (25.0)	
Hemodialysis	6	6 (100.0)	0 (0.0)	

Values are expressed as *N* (%)
TZP piperacillin/tazobactam, *CrCl* creatinine clearance, *IBW* ideal body weight, *LBW (1976)* lean body weight published in 1976, *LBW (2005)* lean body weight published in 2005, *CG IBW* Cockcroft-Gault equation with IBW as a weight parameter, *CG LBW (1976)* Cockcroft-Gault equation with LBW (1976) as a weight parameter, *CG LBW (2005)* Cockcroft-Gault equation with LBW (2005) as a weight parameter

Table 4. Initial daily dose of TZP based on various body size descriptor equations.

CrCl (mL/min)	No. of prescriptions	4.5g, N (%)	6.75g, N (%)	9g, N (%)	13.5g, N (%)	18g, N (%)	*p* Value
CG IBW							
> 40	67	0 (0.0)	1 (1.5)	1 (1.5)	64 (95.5)	1 (1.5)	< 0.001
20-40	27	0 (0.0)	2 (7.4)	9 (33.3)	16 (59.3)	0 (0.0)	
< 20	2	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)	0 (0.0)	
Hemodialysis	6	1 (16.7)	4 (66.6)	1 (16.7)	0 (0.0)	0 (0.0)	
CG LBW (1976)							
> 40	65	0 (0.0)	1 (1.5)	1 (1.5)	62 (95.5)	1 (1.5)	< 0.001
20-40	28	0 (0.0)	2 (7.1)	8 (28.6)	18 (64.3)	0 (0.0)	
< 20	3	0 (0.0)	1 (33.3)	1 (33.3)	1 (33.3)	0 (0.0)	
Hemodialysis	6	1 (16.7)	4 (66.6)	1 (16.7)	0 (0.0)	0 (0.0)	
CG LBW (2005)							
> 40	62	0 (0.0)	1 (1.6)	1 (1.6)	59 (95.2)	1 (1.6)	< 0.001
20-40	30	0 (0.0)	2 (6.7)	7 (23.3)	21 (70.0)	0 (0.0)	
< 20	4	0 (0.0)	1 (25.0)	2 (50.0)	1 (25.0)	0 (0.0)	
Hemodialysis	6	1 (16.7)	4 (66.6)	1 (16.7)	0 (0.0)	0 (0.0)	

Values are expressed as *N* (%)
TZP piperacillin/tazobactam, *CrCl* creatinine clearance, *IBW* ideal body weight, *LBW (1976)* lean body weight published in 1976, *LBW (2005)* lean body weight published in 2005, *CG IBW* Cockcroft-Gault equation with IBW as a weight parameter, *CG LBW (1976)* Cockcroft-Gault equation with LBW (1976) as a weight parameter, *CG LBW (2005)* Cockcroft-Gault equation with LBW (2005) as a weight parameter

prescriptions, respectively. When CrCl > 40 mL/min, almost all of prescriptions used 4.5 g TZP, which is appropriate for an initial dose (2.25 g TZP was used in two instances). When CrCl was between 20-40 mL/min, 4.5 g TZP was written as an initial dose more often than 2.25 g TZP, and when CrCl was less than 20 mL/min, 2.25 g TZP was used as the initial dose more often than 4.5 g TZP. For hemodialysis, only 2.25 g TZP was prescribed.

Table 4 shows the appropriate initial total daily dose of TZP based on various body size descriptor equations. Among 102 prescriptions, 13.5 g TZP was administered as an initial total daily dose in 81 prescriptions. When CrCl > 40 mL/min, 18 g TZP was used in one prescription, and there was one prescription where 6.75 g or 9 g TZP was administered against the recommended TZP dose. In the case of CrCl levels between 20-40 mL/min, 13.5 g was administered more often than 9 g TZP; however, there were two instances where 6.75 g TZP was inconsistent with the recommended TZP dose. When CrCl < 20 mL/min, 13.5 g TZP was used in one prescription, inconsistent with the recommended TZP dose. For the hemodialysis group, 9 g TZP was consistent with the recommended Korean TZP dose as written for one prescription, and 4.5 g and 6.75 g TZP were consistent with non-Korean recommended TZP doses in one and four prescriptions, respectively. An initial total daily dose of 18 g TZP was not prescribed in patients with CrCl of 20-40 mL/min; neither 13.5 g nor 18 g TZP as an initial total daily dose was administered in patients with hemodialysis.

Table 5. Dose of TZP during the treatment based on various body size descriptor equations.

CrCl (mL/min)	No. of prescriptions	2.25g, N (%)	4.5g, N (%)	*p* Value
CG IBW				
> 40	50	2 (4.0)	48 (96.0)	< 0.001
20-40	27	10 (37.0)	17 (63.0)	
< 20	2	2 (100.0)	0 (0.0)	
CG LBW (1976)				
> 40	49	2 (4.1)	47 (95.9)	< 0.001
20-40	28	10 (35.7)	18 (64.3)	
< 20	2	2 (100.0)	0 (0.0)	
CG LBW (2005)				
> 40	46	2 (4.3)	44 (95.7)	< 0.001
20-40	31	10 (32.3)	21 (67.7)	
< 20	2	2 (100.0)	0 (0.0)	

Values are expressed as *N* (%)
TZP piperacillin/tazobactam, *CrCl* creatinine clearance, *IBW* ideal body weight, *LBW (1976)* lean body weight published in 1976, *LBW (2005)* lean body weight published in 2005, *CG IBW* Cockcroft-Gault equation with IBW as a weight parameter, *CG LBW (1976)* Cockcroft-Gault equation with LBW (1976) as a weight parameter, *CG LBW (2005)* Cockcroft-Gault equation with LBW (2005) as a weight parameter

Table 6. Daily dose of TZP during the treatment based on various body size descriptor equations.

CrCl (mL/min)	No. of prescriptions	6.75g, N (%)	9g, N (%)	13.5g, N (%)	18g, N (%)	*p* Value
CG IBW						
> 40	50	1 (2.0)	1 (2.0)	47 (94.0)	1 (2.0)	
20-40	27	1 (3.7)	9 (33.3)	17 (63.0)	0 (0.0)	< 0.001
< 20	2	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	
CG LBW (1976)						
> 40	49	1 (2.0)	1 (2.0)	46 (93.9)	1 (2.0)	
20-40	28	1 (3.6)	9 (32.1)	18 (64.3)	0 (0.0)	< 0.001
< 20	2	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	
CG LBW (2005)						
> 40	46	1 (2.2)	1 (2.2)	43 (93.4)	1 (2.2)	
20-40	31	1 (3.2)	9 (29.0)	21 (67.8)	0 (0.0)	< 0.001
< 20	2	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	

Values are expressed as *N* (%)
TZP piperacillin/tazobactam, *CrCl* creatinine clearance, *IBW* ideal body weight, *LBW (1976)* lean body weight published in 1976, *LBW (2005)* lean body weight published in 2005, *CG IBW* Cockcroft-Gault equation with IBW as a weight parameter, *CG LBW (1976)* Cockcroft-Gault equation with LBW (1976) as a weight parameter, *CG LBW (2005)* Cockcroft-Gault equation with LBW (2005) as a weight parameter

Appropriate TZP dose during the treatment based on renal functions

The appropriate single dose and total daily dose of TZP during treatment was analyzed according to renal function. In this study, “during treatment” was defined as the 2nd or 3rd day of TZP administration. There were 23 patients with no measured SCr or under hemodialysis. Thus, 79 prescriptions were used to evaluate the appropriate single dose and total daily dose of TZP during treatment based on renal functions.

Table 5 presents the appropriate TZP doses under treatment based on various body size descriptor equations. Out of 79 prescriptions, 2.25 g and 4.5 g TZP was used for a single dose under treatment in 14 and 65 prescriptions, respectively. When CrCl > 40 mL/min, almost all patients received 4.5 g TZP as a single dose under treatment in accordance with Korean and non-Korean recommended TZP doses; however, 2.25 g TZP was inconsistent with the recommended TZP dose in two instances. In case of CrCl levels between 20-40 mL/min, there were more prescriptions where 4.5 g TZP was administered based on the Korean recommended TZP dosage, but when CrCl < 20 mL/min, 2.25 g TZP was administered in accordance with non-Korean recommended TZP doses.

Table 6 summarizes the appropriate total daily dose of TZP under treatment based on various body size descriptor equations. In 64 out of 79 prescriptions 13.5 g TZP was used. For CrCl > 40 mL/min, 18 g TZP was used in one instance, and 6.75 g and 9 g TZP (inappropriate for a patient with CrCl > 40 mL/min) were used in one instance each. TZP 13.5 g (appropriate for patients with CrCl levels between 20-40 mL/min) was administered more often than 9 g TZP. For one patient with a CrCl level between 20-40 mL/min, 6.75 g TZP was inappropriately used. For CrCl < 20 mL/min, 6.75 g or 9 g TZP was prescribed in accordance with Korean and non-Korean recommended TZP doses. A total daily dose 18 g TZP was not prescribed for patients with CrCl of 20-40 mL/min, nor was a total daily dose of 13.5 g or 18 g TZP administered in patients with CrCl < 20 mL/min.

DISCUSSION

In general, obesity-related pharmacokinetic parameters, such as volume of distribution and increase in clearance rate, may change such that a higher than average dose is necessary for effective TZP administration.[3,29] Furthermore, patients with obesity show degraded kidney function, which means that appropriate TZP doses based on the renal function of these patients is essential in order to improve the quality of medical treatment and minimize side effects.[8] To our knowledge, studies on appropriate TZP doses for obese patients with cancer have been rare in Korea, which lends further meaning to our study that analyzes this specific patient group.

Contrary to previous studies, our study used appropriate equations to adjust the weight of obese patients.[2,11,15,19-21] The adjusted weights of the patients were calculated using IBW, LBW (1976), and LBW (2005), and the CrCl levels calculated with CG

IBW, CG LBW (1976), and CG LBW (2005) were classified into four predetermined stages according to renal function. There were no statistically significant differences between CG IBW, CG LBW (1976), and CG LBW (2005). Specifically, the mean CrCl level using the CG LBW (2005) equation was lower compared to those using CG IBW and CG LBW (1976) equations. However, according to a study conducted by Demirovic *et al*., the mean CrCl level using LBW (2005) was higher than that of IBW, which is contrary to the results from our study.[19] The contrast between these two studies may be due to the difference in study subject BMIs (BMI ≥ 30 kg/m^2 versus BMI ≥ 40 kg/m^2, respectively).

It is important to measure exact renal function in patients with obesity in order to adjust the doses of medications eliminated through the kidneys, including TZP. According to a study targeted toward extremely obese patients (BMI ≥ 40 kg/m^2), the CrCl levels acquired by substituting LBW (2005) into the CG equation corrected the difference between estimated and actual renal function.[19] However, since the subjects included in the aforementioned study were restricted to extremely obese patients, the application to other patient groups may be limited. Also, in a study published in 2012 showed that calculating CrCl levels with various weight adjustment equations according to BMI values may reduce the difference between estimated and actual CrCl levels.[20] Therefore, it is necessary to perform a prospective clinical study to determine the exact weight adjustment equation through comparison of measured CrCl levels with estimated CrCl levels by using various weight adjustment equations.

TZP dosage varied depending on renal function and indications, but in general, 3.375 g and 4.5 g TZP were administered IV over 30 minutes every 6 and 6-8 hours, respectively.[1,2] However, TZP dosage in Korea is different than that used in America and Europe.[1,2,9] Specifically, when CrCl > 40 mL/min, there was no difference between Korean and non-Korean recommended total daily doses of TZP for all indications, except empirical treatments for patients with febrile neutropenia.[2,9] To cure patients with febrile neutropenia, 13.5 g TZP per day was recommended in other countries, but 18 g TZP per day was suggested in Korea. In addition, the difference in recommended daily doses of TZP was significant when patient renal function was degraded; for most indications (except nosocomial pneumonia), the recommended daily dose of TZP in Korea was relatively higher than recommendations from other countries.[1,2,9] For example, when CrCl levels fall between 20-40 mL/min, package inserts for TZP in Korea recommend doses 4.5 g greater than those recommended in other countries. For hemodialysis, the recommended daily dose of TZP (not including supplementary doses after hemodialysis) in Korea and other countries are 9 g and 4.5 g respectively, which indicates a two-fold difference. This may result from different infusion types (e.g., continuous [over 24 hours], prolonged [over 4 hours] or intermittent [over 30 minutes]) as reported in the study.[34] However, it is necessary to modify and classify Korean recommended TZP doses according to kidney function and indications by comparing TZP dosage in Korea with those from other countries, including America and Europe. It is thought that the 6-hour dosing interval for TZP is more appropriate than the 8-hour dosing interval since β-lactams, such as TZP, are time-dependent antibiotics whose concentrations should exceed minimum inhibitory concentrations (MICs) over 50% of dosing intervals in order to optimize pharmacodynamic effects.[33]

Based on the initial TZP dose analysis, for CrCl levels > 40 mL/min, 4.5 g TZP was used in all prescriptions (excluding two prescriptions). We found that an appropriate initial TZP dose was administered to most of the patients. For CrCl levels between 20-40 mL/min, an initial dose of 4.5 g TZP is recommended in Korea and 2.25 g TZP in other countries; therefore, if an initial TZP dose were administered to patients based on a Korean recommendation, patients in Korea would receive twice the recommended dose than patients in other countries.[1,2,9] According to the initial TZP dose analysis in this group, twice the number of patients was injected with 4.5 g TZP for an initial dose, not 2.25 g TZP. However, this study did not evaluate how TZP dose differences affect the treatment of patients with degraded kidney functions. This point should be addressed in future studies.

Our study has some limitations that should be addressed. This study was conducted retrospectively through electronic patients' medical records, and the appropriate TZP dosing under treatment was determined based on whether or not SCr existed on the 2nd or 3rd day after the initiation of TZP; this could affect assessment of the appropriate TZP dosing under treatment. In this study, the obesity of patients with cancer under TZP during the study period was determined based on the obesity criteria from the World Health Organization. However, these criteria are different from the Korean Society for the Study of Obesity criteria, such that the results from this study may differ from the patient's original obesity rates. Lastly, when SCr values were less than 1 mg/dL in patients aged ≥ 65 years, those were rounded to 1 mg/dL. However, it was found that if CrCl values

were calculated with SCr of 1 mg/dL when SCr values were less than 1 mg/dL, its accuracy did not improve.[11] Therefore, further studies on this point are required.

CONCLUSION

This study is significant in that appropriate TZP dosing was retrospectively analyzed according to renal functions evaluated through various weight adjustment equations (i.e., IBW, LBW (1976), and LBW (2005)) in Korean obese patients with cancer. It was revealed that the appropriate doses of TZP were administered to almost all obese patients with cancer; however, when 20 mL/min ≤ CrCl ≤ 40 mL/min, the recommended TZP dose was different between Korea and other countries by twice the amount, such that careful monitoring of TZP injection in this group of patients is required. Since this study was implemented in a Korean single tertiary hospital, it is likely that applying these results into other institutes will be difficult. Further well-designed, prospective, large-scale studies are necessary to clearly determine the general application of this study's conclusion. In addition, it is possible to create the renal function-based dosing formula for TZP in obese patients with cancer based on the results from this study and future studies that will be conducted at other hospitals, which may help improve antimicrobial treatment for these patients in clinical practice and design and develop new TZP formulations for them in pharmaceutical industry.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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