Research Article

Central nervous system adverse effects of ertapenem in diabetic foot ulcer patients

P. Maheshwari*, S. Nirenjen, R. V. Bibibergin, Thabitha Kumari, T. S. Shanmugarajan, P. Shanmugasundaram

ABSTRACT

Objectives: The objective of the study was to study the effect of ertapenem on central nervous system (CNS) and to study definite, probable, and possible CNS effects associated with ertapenem use. **Materials and Methods:** A total of 63 patients were in ertapenem therapy. Patients were divided into three groups. Provided with case pro forma and Naranjo probability scale, definite, probable, and possible effects are evaluated. Assessment of outcome will be done statistically among Group A, Group B, and Group C which consists of people given ertapenem for 3 days, 5 days, and 7 days, respectively. Moreover, the withdrawal effects of same groups will also be recorded after withdrawal of drug using Naranjo probability scale. Patients of the age group of 30–85 years diagnosed with diabetic foot ulcer and cellulitis. **Results:** The total number of 63 patients on ertapenem therapy was divided into three categories and had a total of 44 male and 19 female patients. Higher number of patients involved in this study was among the age group of 60 years. In this study, outdoor workers and people in rural population were affected more and I found that patients on ertapenem therapy for a lesser number of days had possibly less ADR and those on ertapenem therapy for more than a week had a definite and serious ADR. **Conclusion:** This study concluded that even though ertapenem furnishes a great effect on complicated infections. It has various adverse effects such as hallucinations, delusions, seizures, confusion, altered mental status, and some allergic reactions. On the other hand, withdrawal of ertapenem will subside the acquired adverse effects. Therefore, care must be taken while administering ertapenem and awareness must be created among the patients to avoid unwanted examinations or hospitalizations regarding altered mental status.

KEY WORDS: Adverse effects of ertapenem, Central nervous system, Diabetic foot ulcer

INTRODUCTION

Ertapenem is often used for complicated intra-abdominal and skin structure infections as a result of susceptible organisms.[1] It is unique among the carbapenems due to its high protein binding (85–95%) and comparatively long half-life (4 h), which makes it conducive to home intravenous therapy.[1-3] The extent to which ertapenem distributes into the cerebrospinal fluid (CSF) in humans is unknown. Carbapenems are known to cause neurotoxicity in the central nervous system (CNS), similar to other beta-lactams.[4] Risk factors for carbapenem neurotoxic adverse reactions include the following:(1) Basicity strength of the C-2 amino group for carbapenems; (2) accumulation in the CNS, specifically in cases of excessive dosage or impaired renal clearance; and (3) patients with CNS disorders (e.g., medical history of seizure disorder) Table 1.[5-7]

It has been postulated that carbapenems have discordant rates of neurotoxic adverse reactions potentially due to structural differences within side chains. Available data demonstrate such neurotoxic mechanism through interactions with the γ-aminobutyric acid receptor A ($GABA_A$) Table 2.[1,8] This interaction is through the side chain on the second carbon atom (C-2) in the carbapenem nucleus. A carbapenem with a basic C-2 side chain increases the binding to $GABA_A$ resulting in higher neurotoxic activity in animal models Table 3.[1,9] Even though ertapenem has an acidic carboxyl group at the C-2 position and the lowest binding capacity to $GABA_A$ than compared to other carbapenem drugs, it shows certain potential neurotoxic activity.[10]

However, clinical studies supporting the claim of ertapenem use associated with CNS effects are limited.[3] Hence, this study was designed to determine

Access this article online

Website: jprsolutions.info | ISSN: 0975-7619

Department of Pharmacy Practice, School of Pharmaceutical Sciences, Vels University, Chennai, Tamil Nadu, India

***Corresponding author:** Ms. P. Maheshwari, Department of Pharmacy Practice, School of Pharmaceutical Sciences, Vels University, Velan Nagar, P. V. Vaithiyalingam Road, Pallavaram, Chennai - 600 117, Tamil Nadu, India. E-mail: mahe.mpharm@gmail.com

Received on: 14-05-2019; Revised on: 23-07-2019; Accepted on: 27-08-2019

the relationship between the use of ertapenem and various neurotoxicity effects due to the same in CNS.[8]

Ertapenem is a carbapenem used to treat a variety of infections including complicated skin and skin structure and intra-abdominal infections caused by susceptible strains of *Staphylococcus aureus*, streptococci, *Enterobacteriaceae*, and anaerobes. Convenient once-daily dosing makes ertapenem well suited to home intravenous therapy and nursing home administration. However, CNS toxicity has been reported with the carbapenem class of beta-lactam antimicrobials despite appropriate dosing.[9]

Ertapenem is approved for parenteral use in patients with complicated intra-abdominal infection (cIAI), community-acquired pneumonia (CAP), and acute pelvic infection caused by susceptible strains of certain designated organisms in both the US and the EU. Additional approved indications in the US include complicated skin and skin structure infection (cSSSI) and complicated urinary tract infection (cUTI).[9]

Ertapenem has a broad spectrum of *in vitro* activity against Gram-negative pathogens including extended-spectrum β-lactamase-and AmpC-producing *Enterobacteriaceae*, Gram-positive pathogens, and anaerobic pathogens. It has similar efficacy to comparator antibacterials such as piperacillin/tazobactam in cSSSI (including diabetic foot infection), cIAI, and acute pelvic infection and ceftriaxone with or without metronidazole in cIAI, cUTI, and CAP. The drug has also shown efficacy in the treatment of pediatric patients with complicated community-acquired bacterial infections. Ertapenem has a convenient once-daily administration schedule and is generally well tolerated. Thus, ertapenem is an important option for the empirical treatment of complicated community-acquired bacterial infections in hospitalized patients.[1]

At their most simple level, all β-lactam antibiotics exert their antibacterial action by chemically acylating an active-site serine residue on a target bacterial penicillin-binding protein (PBP). The resulting covalently modified enzyme is stable and, therefore, unable to complete its biological function, in this case, the transpeptidation of peptidoglycan to form a structurally stable bacterial cell wall. Ertapenem, for example, has excellent affinity for a number of the essential PBPs in *Escherichia coli*, in particular, PBP2 (IC50 0.01 mg/L) and PBP3 (IC50 0.04 mg/L), consistent with its excellent *in vitro* activity against this organism (IC50 is the concentration of test drug necessary to inhibit by 50% the labeling of [3H] penicillin to requisite PBP in an *E. coli* membrane preparation). With regard to PBP2, ertapenem has similar potency to imipenem and is 30-fold more potent than ceftriaxone; with regard to PBP3, ertapenem is similar in potency to ceftriaxone and is 60-fold more potent than imipenem.[9] It should be noted that ertapenem, like all marketed β-lactams, has little affinity for *Staphylococcus aureus* PBP2a, the expression of which mediates methicillin resistance in staphylococci.[1]

Table 1: Gender-wise distribution

Sex	Number of patients (n=63)	Percentage of patients
Male	44	69.84
Female	19	30.16

Table 2: ADRs of ertapenem

Number of days given	3 days	5 days	7 days
Number of patients	22	24	17
Hallucination (%)	27.273	37.5	70.58
Seizure (%)	4.545	16.667	35.29
Altered mental status (%)	13.636	25	76.47
Allergic reactions (%)	4.545	25	47.05

MATERIALS AND METHODS

A total of 63 patients were in ertapenem therapy. Patients were divided into three groups. Provided with case pro forma and Naranjo probability scale, definite, probable, and possible effects are evaluated. Assessment of outcome will be done statistically among Group A, Group B, and Group C which consists of people given ertapenem for 3 days, 5 days, and 7 days, respectively. Moreover, the withdrawal

Table 3: After withdrawal of ertapenem

Number of days after withdrawal		1	2	3	4	5	6	7	8	9	10
Hallucination	3 days	5	2	1	-	-	-	-	-	-	-
	5 days	6	3	2	1	-	-	-	-	-	-
	7 days	9	9	7	5	4	4	3	1	-	-
Seizure	3 days	-	-	-	-	-	-	-	-	-	-
	5 days	1	1	-	-	-	-	-	-	-	-
	7 days	3	3	2	1	-	-	-	-	-	-
Altered mental status	3 days	2	1	-	-	-	-	-	-	-	-
	5 days	4	4	3	1	-	-	-	-	-	-
	7 days	8	8	6	5	4	2	1	-	-	-
Allergic reactions	3 days	1	-	-	-	-	-	-	-	-	-
	5 days	4	2	1	-	-	-	-	-	-	-
	7 days	6	6	4	3	3	1	-	-	-	-

effects of same groups will also be recorded after withdrawal of drug using Naranjo probability scale. Patients of the age group of 30–85 years diagnosed with diabetic foot ulcer and cellulitis according to Infectious Disease Society of America guidelines and on treatment with ertapenem for 3 ± 1 days will be included in the study after receiving informed consent form approved by IEC from them. Patients diagnosed with diabetic foot ulcer and cellulitis and are not on ertapenem therapy, patients with significant renal impairment expressed in terms of eGFR <40 min/h, patients with hepatic impairment or any other disease condition that can cause ertapenem toxicity, patients those are on other beta-lactam antibiotics that may cause CNS disturbances, pregnant and lactating women., and psychiatric patients and those who are not able to provide with informed consent form.

Statistical Analysis (Describe Plan for Analyzing the Primary Endpoint)

The statistical analysis used in this study was done with IBM SPSS version 23. Descriptive summary statistics are presented as mean (SD) or median (minimum, maximum) 95% confidence level is maintained to minimize type1 error and type 2 error. Hence, $P < 0.05$ was considered statistically significant. Chi-square test was used for assessing depression. Student's *t*-test was used for comparison of mean value of selected variables.

RESULTS

The total number of 63 patients on ertapenem therapy was divided into three categories and had a total of 44 male and 19 female patients. Higher number of patients involved in this study was among the age group of 60 years. In my study, outdoor workers and people in rural population were affected more and I found that patients on ertapenem therapy for a lesser number of days had possibly less ADR and those on ertapenem therapy for more than a week had a definite and serious ADR which was significant with "*P*" = 0.03 as mentioned in the previous study. Patients were divided into three categories among which 22 patients received ertapenem for 3 days, 24 people received ertapenem for 5 days, and 17 people received the drug for 7 days. The people on ertapenem therapy for 7 days are more prone to get probable neurotoxic effects of the drug comparing the people given with 5 days and 3 days. Withdrawal of ertapenem shows an immediate resolute from the ADR of 3 days for patients taking 3 days therapy and for those taking ertapenem therapy for 5 days get resolved in 4 days after withdrawal. Finally, there is a gradual resolute of 8 days for patients taking ertapenem 7 days therapy.

CONCLUSION

This study concluded that even though ertapenem furnishes a great effect on complicated infections. It has various adverse effects such as hallucinations, delusions, seizures, confusion, altered mental status, and some allergic reactions. On the other hand, withdrawal of ertapenem will subside the acquired adverse effects. Therefore, care must be taken while administering ertapenem and awareness must be created among the patients to avoid unwanted examinations or hospitalizations regarding altered mental status.

REFERENCES

1. Miller AD, Ball AM, Bookstaver PB, Dornblaser EK, Bennett CL. Epileptogenic potential of carbapenem agents: Mechanism of action, seizure rates, and clinical considerations. Pharmacotherapy 2011;31:408-23.
2. Merck and Co., Inc. Invanz (ertapenem) Package Insert. Whitehouse Station, New Jersey: Merck and Co., Inc.; 2011.
3. Shah PM, Isaacs RD. Ertapenem, the first of a new group of carbapenems. J Antimicrob Chemother 2003;52:538-42.
4. Sunagawa M, Matsumura H, Sumita Y, Nouda H. Structural features resulting in convulsive activity of carbapenem compounds: Effect of C-2 side chain. J Antibiot (Tokyo) 1995;48:408-16.
5. Schliamser SE, Cars O, Norrby SR. Neurotoxicity of beta-lactam antibiotics: Predisposing factors and pathogenesis. J Antimicrob Chemother 1991;27:405-25.
6. Calandra G, Lydick E, Carrigan J, Weiss L, Guess H. Factors predisposing to seizures in seriously ill infected patients receiving antibiotics: Experience with imipenem/cilastatin. Am J Med 1988;84:911-8.
7. Chow KM, Szeto CC, Hui AC, Li PK. Mechanisms of antibiotic neurotoxicity in renal failure. Int J Antimicrob Agents 2004;23:213-7.
8. Hikida M, Masukawa Y, Nishiki K, Inomata N. Low neurotoxicity of LJC 10,627, a novel 1 beta-methyl carbapenem antibiotic: Inhibition of gamma-aminobutyric acidA, benzodiazepine, and glycine receptor binding in relation to lack of central nervous system toxicity in rats. Antimicrob Agents Chemother 1993;37:199-202.
9. Norrby SR. Neurotoxicity of carbapenem antibiotics: Consequences for their use in bacterial meningitis. J Antimicrob Chemother 2000;45:5-7.
10. Oo Y, Packham D, Yau W, Munckhof WJ. Ertapenem-associated psychosis and encephalopathy. Intern Med J 2014;44:817-9.

Source of support: Nil; Conflict of interest: None Declared