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Case Report Open Access

Ertapenem-induced Neuropsychiatric Symptoms in an Elderly Patient with Chronic Kidney Disease Resulting to a Prescribing Cascade

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Abstract

Seizure as a rare but a major side-effect of carbapenems are widely reported in literature but non-seizure, neuropsychiatric events have scarce, limited information available.

Objectives: To present a case report of an elderly patient with chronic kidney disease who had neuropsychiatric effects during ertapenem therapy leading to additional prescribing of anti-psychotic/sedating medications to manage adverse drug events.

We present a case of an 85 year old female patient without prior CNS disorder who developed visual hallucinations, agitation, disorientation, sleeplessness after 3 days of ertapenem 1 g therapy. The patient was prescribed with quetiapine and valproic acid to initially manage restlessness and donepezil was later added. Ertapenem was discontinued after day 7 of therapy while agents to manage agitation were continued. Based on the Naranjo score (6), the manifestations of hallucinations, agitation, sleeplessness were probable adverse drug reactions of ertapenem. Associated risk factors were excessive dose, advanced age and renal dysfunction. With a creatinine clearance of 30 ml/min, the recommended dose is 500 mg daily. Two days after ertapenem was discontinued, the symptoms abated. There was a noted decrease of hallucination, disorientation, restlessness and patient was slowly able to sleep. On the 13th hospitalization day, there was no restlessness, only episodes of confusion. Patient was discharged on the 15th hospitalization day with discharge medications for valproic acid, donepezil and alprazolam.

Conclusion: Ertapenem may exhibit non-seizure neurotoxicity if used beyond recommended dose. Adverse drug events from inappropriate use of drug are associated with patient harm, longer hospitalization and more medications which we were preventable in the first place. To our knowledge, this is the first probable adverse drug reaction from ertapenem documented in the Philippine setting.

Introduction

A major but rare side-effect of carbapenems is neurotoxicity. It can range from seizures to non-seizure toxicity (agitation, hallucination, delirium, etc.) It is estimated that carbapenem-induced seizure is most with imipenem-cilastin (3-33%) [1], but the remaining (doripenem, meropenem, ertapenem) have a prevalence of less than 1%. Seizure as an adverse drug reaction is highly documented. On the other-hand, non-seizure toxicity (hallucinations, agitation) has limited information. There is no established prevalence rate due to a small population of patients documented from post-marketing surveillance. However, generalized altered mental status due to ertapenem has a prevalence of 3.1 to 5.3% [2].

A prescribing cascade refers to the situation when a new medicine is prescribed to 'treat' an adverse reaction to another drug due to the belief that a new medical condition requiring treatment has developed [3]. Prescribing cascade can result to adverse outcomes. It is possible that the second drug will increase the severity of the adverse reaction to the first drug or when the second drug places the patient at risk of additional adverse drug reactions.

Elderly patients are prone to prescribing cascades. Factors such as polypharmacy, gender, use of high alert medications, comorbidities and age-related physiological decline contribute to the higher risk of adverse drug reactions. To avoid prescribing cascades, early detection of adverse drug events and recognition of potential to cause adverse drug reactions are important.

Objectives

To present a case report of a patient who had neuropsychiatric effects during ertapenem therapy leading to additional prescribing of anti-psychotic/sedating medications to manage side/effects.

Case Report

We present a case of an 85 year old female patient (estimated height 155 cm, ideal body weight) with history of recurring urinary tract infection, hypertensive cardiovascular disease, bronchial asthma and chronic kidney disease but without prior CNS disorder. One month prior to admission, he was admitted for 8 days for urinary tract infection where urine culture revealed extended-spectrum beta-

lactamase producing Kleibsella pneumoniae susceptible to meropenem. During this admission, patient came due to painful urination. Three days earlier, the private duty nurse of the patient noted increased sleeping time for which she sought consultation. Initial urinalysis showed 17 WBC/HPF and patient was initiated with ertapenem 1 g every 24-hours to run for 30 minutes. On the day of admission, patient came to the hospital and urine culture revealed again extended-spectrum beta-lactamase producing *Kleibsella pneumoniae* at 100,000 colonies/ml sensitive to ertapenem. Ertapenem prescription was continued and already on day 3 during time of admission. It was dosed at 1 g every 24-hours to be infused for 30 minutes. There were no other drugs prescribed but maintenance medications were ordered to be continued. Analysis shows no uricosuric medication on the list. Most are cardiovascular drugs. On Day 4 of ertapenem therapy, doctor's progress notes record of visual hallucination. On the following day, visual hallucination was still noted along with difficulty of sleeping. Clonazepam was prescribed to induce somnolence. Later in the day, patient became incoherent. On day 5 of ertapenem therapy, visual hallucination was still present with disorientation (to place and time but not in person) and difficulty of sleeping. Later, the patient was not able to follow commands and with incoherent speech. The case was referred to a neurologist for which quetiapine 12.5 mg and valproic acid 250 mg was prescribed to manage the restlessness. The following day, less hallucinations but disorientation and incoherent speech were noted. Patient was still restless. Donepezil 5 mg at bedtime was added. Ertapenem was discontinued after seven days which is also the 5th hospital day. Nitrofurantoin was prescribed as step-down therapy. After discontinuing ertapenem, patient had longer sleeping hours with more comprehensible speech but still with episodes of restlessness. As the days went by, patient became more coherent in speech with decreased disorientation. Fragmented sleeping time was still noted. Patient later underwent urethral calibration and cystoscopy for marked urinary retention. Patient had less and less neuropsychiatric manifestations but there were still episodes. Upon discharge, patient was prescribed with alprazolam, valproic acid and donepezil along with bethanecol and nitrofurantoin.

Based on the Naranjo score (6), the manifestations of visual hallucinations, agitation, sleeplessness were probable adverse drug reactions of ertapenem. Associated risk factors were excessive dose, advanced age and renal dysfunction. With a creatinine clearance of 30 ml/min, the recommended dose is 500 mg daily.

Discussion

In general, antibiotics specifically beta-lactam antibiotics have the propensity to cause neurotoxicity. It has been postulated the neurotoxicity (seizure) induced by beta-lactams including carbapenems are related to their interference with the function of the inhibitory neurotransmitter gamma-aminobutyric acid [4]. Risk factors associated with this neurotoxicity include advanced age, history of central nervous system disease, renal insufficiency, as well as low body weight [5]. Seizure as a rare but a major side-effect of carbapenems are widely reported in literature but non-seizure, neurotoxic events have scarce, limited information available. It is estimated that carbapenem-induced seizure is most with imipenem-cilastin (3-33%) [1] but the remaining carbapenems (doripenem, meropenem, ertapenem) have a prevalence of less than 1%. On the other hand, non-seizure toxicity has no prevalence estimate due to a trickle of documented reports involving a small population of patients from post-marketing surveillance.

The epileptogenic potential of the members of the carbapenem class varies from another. It is said to be due to the difference in their chemical structures. Doripenem which exhibits low neurotoxic potential exhibits low affinity to the GABA-A receptor compared with meropenem, imipenem and panipenem [5]. Structure activity relationship reveal that the more basic the side chain of the carbapenem molecule, the more epileptogenic potential there is, due to increased affinity to the GABA-A receptor. The C2 side chain of meropenem is much less basic than those of imipenem and panipenem, and as predicted, the former is less associated with neurotoxic effects than the latter.

Drug-drug interaction with valproic acid and carbapenems are well-documented. Decreased valproate levels can reach up to 90% in days when concomitantly administered with carbapenems [6-11]. The mechanism of the interaction is still to be elucidated but it is thought be related to the decreased enteric hydrolysis of the valproate glucuroniderefer. In this case, the loss of anti-psychotic activity related to valproic acid-ertapenem drug interaction is hard to quantify due to the presence of two other anti-psychotic medications and eventual discontinuation of ertapenem. The symptoms slowly abated after discontinuation of ertapenem. No therapeutic drug monitoring was performed as this service is not available in the laboratory.

Visual hallucinations due to ertapenem is a rare adverse drug event. There are no exact prevalence rate but a literature search in PubMed, Google Scholar (accessed October 20, 2014) reveal less than 5 case reports involving mostly geriatric patients with chronic kidney disease. The mechanism of ertapenem-induced visual hallucination and agitation is unknown and yet unclear whether GABA receptors are involved.

A prescribing cascade occurs when a drug's side-effects or adverse reaction is misdiagnosed as a medical condition which requires further prescription of additional drugs. It can lead to more side-effects to the new drug/s and increase the probability of drug-drug interactions. As polypharmacy is common in the elderly, they are expected to be at high risk for prescribing cascades.

One study (2010) found out that an average 81-year-old is prescribed with about 15 different medications at the same time, ranging from 6 to 28 medications with approximately 8.9 drug-related problems per patient [12]. Another finding is that the elderly consumes the most medications, increasing the probability of a prescribing error. According to Gurwitz et al. [13], the biggest chunk of preventable adverse reactions occurred at the prescribing or monitoring stages. Prescribing errors range from the wrong choice of drug, incorrect dose, inadequate patient education, and prescribing of a drug with a well-known drug interaction with another drug in the patient's therapeutic regimen. If prescribing errors are detected before the drug is administered, there will be a large amount of adverse drug reactions prevented. Deprescribing has been forwarded as a strategy to stop prescribing cascades. It involves decreasing, withdrawing or discontinuing medications.

Ertapenem dosing in chronic kidney disease is important as it is eliminated primarily via renal pathway. According to ertapenem product specification, patients with creatinine clearance >30 mL/min/1.73 m^2 require no dosage adjustment but in adult patients with advanced renal insufficiency (creatinine clearance ≤ 30 mL/min/1.73 m^2), including those on hemodialysis, should receive 500 mg daily.

Albumin levels also influence risk of ertapenem toxicity [14,15]. Ertapenem is highly-protein bound (95%) to albumin. Decreasing albumin levels predispose to drug toxicity as there are more freely circulating ertapenem molecules resulting to increased plasma levels. Only freely available, unbound drugs have a pharmacologic effect. For this patient, there was no albumin test ordered as no indications such as shock or hypovolemia were present. The hemoglobin levels were also normal. It is thus inferred that albumin was not a risk factor for the adverse drug reaction in this patient. Additionally, uricosuric agents also influence ertapenem risk for toxicity. They interfere with the renal excretion of carbapenems resulting to drug accumulation in the kidney or bladder. These patients have no uricosuric drug both in the maintenance and hospital-prescribed medications.

To avoid prescribing cascades, recognition of potential to cause adverse drug reactions are important and early detection are critical.

Conclusion

Neurotoxicity is a rare adverse drug reaction to ertapenem but based on few case reports, it is primarily common in the elderly with chronic kidney disease. Adverse drug events contribute to patient harm, longer hospitalization and more medication costs for the patient especially the vulnerable elderly population. Preventable medication errors should be detected and their potential to induce medication harm should be highlighted. Prescribers should be aware of renal adjusted dosing to prevent harmful side-effects.

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