Journal of Clinical Case Reports

Case Report Open Access

Etoposide-Associated Muscle Cramps and Management with Diazepam

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Abstract

Aim: Etoposide is an anti-neoplastic drug used in the management of testicular malignancies. In this report, we describe an unexpected adverse reaction experienced by a 27-year-old male patient undergoing first line treatment for metastatic testicular cancer with bleomycin, etoposide, and cisplatin (BEP) protocol.

Case Report: The patient, on separate days, experienced two episodes of severe muscle cramps associated with excruciating pain shortly after the administration of etoposide therapy. With no other drugs administered at the time of the etoposide infusions, and a Naranjo probability score of seven, the association between etoposide and the muscle cramps experienced by the patient is probable. To maintain the patient on first-line therapy, diazepam was administered prior to each infusion of etoposide with a favorable response. The patient continued to receive therapy with etoposide without the occurrence of muscle cramps.

Conclusion: To the extent of our knowledge, this is the first case report describing such an adverse reaction, also highlighting a possible means of management.

Keywords: Etoposide; Adverse-drug reaction; Muscle cramps; Diazepam; Testicular cancer

Introduction

Etoposide, also known as VP-16, is a relatively old semisynthetic derivative of podophyllotoxin used in the treatment of various neoplastic diseases. It belongs to the family of drugs called "Topoisomerase II Inhibitors", which includes: teniposide, doxorubicin, daunorubicin, epirubicin, idarubicin and mitoxantrone [1]. Anti-neoplastic effects of etoposide and topoisomerase II inhibitors are cell cycle-dependent, acting primarily during the G2 and S phases of cell replication. Inhibition of topoisomerase II, and its DNA ligating function, leads to inhibition of DNA and cell replication, as well as induction of apoptotic cell death [1,2].

Etoposide may be administered either orally or intravenously (IV), both routes sharing the same side effect profile. With intravenous administration, the average volume of distribution of etoposide ranges between 7-17 L/m^2, and the terminal elimination half-life spans 4-11 hours. Etoposide is metabolized via hepatic *CYP3A4* and *3A5* enzymes and excreted along with its metabolites mainly in urine (56%, 45% unchanged drug), and feces (44%) [3]. Myelosuppression is the most common adverse reaction associated with etoposide and is a dose-limiting toxicity [4]. Other common adverse reactions include nausea, vomiting, hypotension, alopecia, and allergic reactions [2]. Post-marketing side effects have been reported, with case reports describing constipation, diaphoresis, seizures, hypersensitivity and vasospasms associated with etoposide [3].

A thorough review of the literature related to etoposide adverse effects revealed that although vasospasms can happen, muscle spasms have rarely been reported [5-7]. While vasospasms are caused by constriction of blood vessels leading to narrowing of arteries, muscle spasms or cramps are defined as the sudden, involuntary, painful contraction of a muscle or part of it, often accompanied by palpable knotting of the muscle. Muscle spasms are like cramps but may occur without pain and last for a shorter period [8]. This is a report of etoposide-induced muscle cramps.

Case Report

A 27-year-old Iraqi male (70 kg, 170 cm), with a body surface area (BSA) of 1.8 m^2, with left testicular choriocarcinoma and lung metastasis was admitted to the hospital for his initial cycle of first line chemotherapy treatment. The patient was diagnosed in August 2017 after he had noticed unusual scrotal swelling for which he sought medical advice. Investigations revealed a mixed germ cell tumor on the left testicle, 6.5 cm in size, consisting of choriocarcinoma 70%, and seminoma 30%. The tumor was limited to the testes with no lymphovascular invasion. Computed Tomography of the chest showed extensive metastasis to the lungs, mainly on the right side. Left radical orchiectomy was done 7 days prior to the patient's first chemotherapy cycle. The patient's physical exam was only remarkable for the presence of right gynecomastia, with no other complaints. He has no medical co-morbidities and does not take any chronic medications at home.

The patient's chemotherapy plan consisted of four cycles of chemotherapy based on the bleomycin, etoposide, and cisplatin (BEP) protocol. The BEP protocol was administered as listed in the 2017 National Comprehensive Cancer Network (NCCN) guidelines for the management of testicular cancer as a primary chemotherapy regimen for the management of germ cell tumors consisting of: cisplatin 20 mg/m^2 (36 mg) days 1-5, etoposide 100 mg/m^2 (180 mg) days 1-5, and bleomycin 30 units weekly on days 1, 8, and 15 of each cycle, repeated every twenty-one days [9] (Table 1). Bleomycin was given first on day 1, followed by the etoposide infusion administered over 1 hour in 500 mL of normal saline solution (NSS), and once completed, cisplatin in 250 ml NSS was infused over 30 minutes. The hydration that the patient received before and after cisplatin included 1000 ml of NSS infused at a rate of 500 ml/hr with 20 mEq/L of KCL and 1 g/L of $MgSO_4$. All

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Received August 02, 2019; **Accepted** August 12, 2019; **Published** August 19, 2019

Citation: Zaweel A, Karaoui LR, Abi-Nader T, Youssef A, Saad AH (2019) Etoposide-Associated Muscle Cramps and Management with Diazepam. J Clin Case Rep 9: 1270.

medications were administered independently from one another, and no other medications were concurrently administered with the etoposide infusion.

During his first cycle, the patient experienced two episodes of neck muscle cramps associated with severe pain that would occur upon the administration of etoposide. The first episode of muscle cramps occurred on day three of the patient's hospital stay, the third day of chemotherapy administration. Soon after the etoposide infusion was started, the patient began experiencing cramping on the right side of his neck extending down towards his shoulder. The patient was noticeably distressed and described sharp, intolerable pain associated with the cramp, and rated it as 10/10 on the visual analog pain scale. The infusion of etoposide was halted and acetaminophen 1g IV was administered once, lowering the pain to a relatively tolerable level of 5/10 before the etoposide infusion was resumed. At the end of the infusion, the cramp gradually resolved while the pain persisted at the same level (5/10). Later that night, after the muscle cramp had resolved, the pain increased in severity again to 10/10 and tramadol 50 mg was given once orally.

The second episode occurred the fourth day of hospital stay, on day four of chemotherapy administration, also after starting the etoposide infusion. This time, acetaminophen 1 g IV was inadequate in managing the pain which remained unbearable, rating 10/10 on the scale. Morphine sulfate 5 mg subcutaneously (SC) was administered once to continue the etoposide infusion at a relatively tolerable pain level (5/10). On the final day of the cycle (day five of hospital stay), to avoid the cramping, diazepam 5 mg IV as a bolus injection was administered once, 1 hour prior to the etoposide infusion. The patient did not experience any neck cramping, nor pain (0/10), and the etoposide infusion was completed without interruption. No electromyogram testing was completed for this patient during or after any of the muscle cramping episodes.

Based on its success in preventing the neck cramps, diazepam was added to the patient's regimen in subsequent cycles. During his second cycle, diazepam 5 mg IV was administered before each of the etoposide infusions. Etoposide infusion rate was changed to 500 mL NSS over two hours, as opposed to 500 mL NSS over one hour during the first cycle. A standby order was written for morphine sulfate 5 mg SC in case the cramps developed, and prompt pain management was necessary. No cramping occurred at any time during the patient's five-day course at the hospital; morphine was not administered, nor were any other pain interventions necessary.

The patient's third cycle was completed without adverse events as well. However, upon weight and height assessment, the patient was found to have lost 8 Kg (patient's weight decreased from 70 Kg to 62 Kg) between cycles. A new BSA was calculated to be 1.71 m^2, and chemotherapy doses were adjusted accordingly. The patient received cisplatin 20 mg/m^2 (35 mg) IV, and etoposide 100 mg/m^2 (175 mg) IV daily for five days with bleomycin 30 mg IV administered on day one only. Etoposide was infused in 500 mL NSS over two hours and diazepam 5 mg IV was administered once as a bolus injection preceding each infusion. No cramping occurred, and no pain interventions were necessary.

During the patient's fourth and projected final cycle with BEP protocol, the patient was scheduled to receive five days of chemotherapy like his previous cycles. Bleomycin 30 mg IV was administered on day one of the cycle, thus completing the planned bleomycin doses for the BEP protocol. Daily infusions of cisplatin 20 mg/m^2 (35 mg) IV and etoposide 100 mg/m^2 (175 mg) IV were planned for 5 days, with diazepam 5 mg IV to be administered prior to each etoposide infusion. The first two days of therapy were completed without any cramping or pain. However, on the morning of day three, unforeseen family circumstances forcing the patient to arrange travel plans as soon as possible led to the premature termination of the cycle. Before discharge on day three, the patient received a dose of diazepam 5 mg IV followed by etoposide 200 mg IV over one hour, and subsequently cisplatin 100 mg IV over 30 minutes. Despite the increased dose, and shortened infusion time, no cramping occurred during the etoposide infusion and no pain management was necessary.

It is important to note that throughout all the cycles the patient's complete blood count, electrolytes, renal function and urine output were measured and monitored before the initiation of the chemotherapy and then daily. During the four cycles, the patient's electrolytes and renal function remained normal. Particularly, the patient's potassium and magnesium were consistently within the hospital's normal ranges.

During the hospital stay, the patient's antiemetic regimen consisted to fosaprepitant, ondansetron and dexamethasone administered as detailed in Table 1. Upon discharge, after each cycle of chemotherapy, the patient was prescribed a short-term home regimen of anti-emetics and colony stimulating factor (Table 2). Other than these prescribed agents with their specified duration of therapy, the patient did not receive any other medications throughout the four cycles.

Discussion

Testicular cancer is usually considered a curable disease whereby its 5-year survival rate is approximately 95%. However, survival and prognosis highly depend on multiple factors including staging of the disease as well as the type and complications of the treatment. Accordingly, these 5-year survival rate decreases to 80% in patients with stage 4 testicular cancers [10-12].

According to Sattar and colleagues, platinum-based chemotherapy is considered the standard of care in testicular cancer patients and achieves a total response rate estimated to be around 90%. Alopecia was noted to be the most commonly experienced side effect associated with the use of platinum-based chemotherapy in those patients [13]. The use of bleomycin is highly correlated with pulmonary toxicity, also known as "Bleomycin Pulmonary Toxicity" (BPT), which was shown to be associated with a low body mass index (BMI< 22 kg/m^2). However, there was no effect of BPT incidence on survivorship of testicular cancer in men [13,14]. Similarly, Kier and colleagues reported an enhanced survival rate for disseminated germ-cell cancer (GCC) with the use of BEP [14]. Clinical trials have shown no superiority or equivalency in effectiveness and safety of other testicular cancer regimens when compared to BEP. Therefore, BEP remains the preferred regimen for the management of testicular cancer, unless the patient has a compelling indication that prohibits him from receiving it [15,16].

Adverse effects associated with chemotherapy were shown to have an undesirable impact on patients' compliance with their regimens, which in turn can lead to poor patient outcomes. As described by Accordino and Hershman, cancer patients who were non- adherent to their chemotherapy demonstrated inferior survival rates compared to adherent patients [17]. Our patient experienced adverse effects associated with chemotherapy that could have led to the interruption of chemotherapy administration or change to a less effective treatment plan if the adverse effects were not properly managed. In establishing a causal relationship between the cramping experienced by the patient

Cycle 1								
Drug	**Dose/Route**	**Diluent**	**Infusion Time**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day5**
Cisplatinaa	36 mg IV	250 ml NSS	30 min	8:00 PM	4:00 PM	4:00 PM	2:00 PM	2 PM
Etoposide	180 mg IV	500 ml NSS	60 min	6:00 PM	3:00 PM	2:00 PM	12:00 PM	11:00 AM
Bleomycin	30 Units IV	50 ml NSS	30 min	5:30 PM	-	-	-	-
Acetaminophen	1g IV	-	-	-	-	3:00 PM[b]	12:00 PM	-
Tramadol	50 mg IV	-	-	-	-	10:00 PM	-	-
Morphine	5 mg subcutaneously	-	-	-	-	-	12:45 PM[a]	
Cycle 2								
Drug	**Dose/Route**	**Diluent**	**Infusion Time**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day5**
Cisplatin	36 mg IV	250 ml NSS	30 min	3:10 PM	1:30 PM	1:00 PM	11:00 AM	11:00 AM
Etoposide	180 mg IV	500 ml NSS	120 min	3:45 PM	2:15 PM	2:00 PM	11:30 AM	12:00 PM
Bleomycin	20 Units IV	50 ml NSS	10 min	3:00 PM	-	-	-	-
Valium	5 mg IV	-	-	3:40 PM	2:00 PM	2:00 PM	11:30AM	12:00PM
Cycle 3								
Drug	**Dose/Route**	**Diluent**	**Infusion Time**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day5**
Cisplatin	35 mg IV	250 ml NSS	30 min	4:00 PM	3:00 PM	1:00 PM	1:00 PM	11:00 AM
Etoposide	175 mg IV	500 ml NSS	120 min	5:00 PM	4:00 PM	2:00 PM	2:00 PM	12:00 PM
Bleomycin	30 Units IV	50 ml NSS	10 min	3:00 PM	-	-	-	-
Valium	5 mg IV	-	-	4:00 PM	3:00 PM	2:00 PM	2:00 PM	11:00 AM
Cycle 4								
Drug	**Dose/Route**	**Diluent**	**Infusion Time**	**Day 1**	**Day 2**			
Cisplatin	35 mg IV	250 ml NSS	30 min	5:00 PM	5:00 PM			
Etoposide	175 mg IV	500 ml NSS	120 min	3:00 PM	2:00 PM			
Bleomycin	30 Units IV	50 ml NSS	10 min	6:00 PM	-			
Valium	5 mg IV	-	-		7:00 AM			
Cycle 4-Day 3								
Drug	**Dose/Route**	**Diluent**	**Infusion Time**	**Day 3**				
Cisplatin	100 mg IV	250 ml NSS	30 min	8:00 AM				
Etoposide	200 mg IV	500 ml NSS	60 min	7:00 AM				
Valium	5 mg IV	-	-	7:00 AM				
Antiemesis[c]								
Drug	**Dose/Route**	**Frequency**						
Fosaprepitant	150 mg IV	On day 1 only						
Metoclopramide	10 mg IV	Every 6 hours as needed						
Methylprednisolone	60 mg IV	Daily						
Ondansetron	8 mg IV	Every 12 hours						

[a]Hydration before and after cisplatin included 1000 ml of NSS infused at a rate of 500 ml/hr with 20 mEq/L of KCL and 1 g/L of $MgSO_4$.
[b]Acetaminophen and morphine were ordered STAT and so the times stated may not accurately reflect the time administered; the drug may have been administered before being recorded in the nurse log books.
[c]Antiemesis regimen remained the same throughout the cycles, started on the same day as chemotherapy and continued until day 5.

Table 1: Medication regimen.

Discharge Cycles 1, 2, 3			
Drug	**Dose/Route**	**Frequency**	**Duration**
Metoclopramide	10 mg PO	Every 8 hours as needed	6 days
Ondansetron	8 mg PO	Every 12 hours	3 days
Filgrastim	300 mcg SC	Daily	6 days
Discharge Cycle 4			
Drug	**Dose/Route**	**Frequency**	**Duration**
Metoclopramide	10 mg PO	Every 8 hours as needed	5 days
Ondansetron	8 mg PO	Every 12 hours	4 days
Filgrastim	300 mcg SC	Daily	5 days
Desloratadine	5 mg	Daily	5 days

Table 2: Discharge regimen.

and the administration of etoposide, the "Naranjo Adverse Drug Reaction Probability Scale" was used. The Naranjo Scale estimates the probability that a certain adverse reaction is related to a specific drug by calculating a score using a set of inputs [18]. The total score calculated for etoposide-associated neck cramps was seven, ruling out other alternatives and considering that etoposide, on two separate occasions, was the sole medication administered prior to the onset of cramps, and that the cramps resolved after discontinuation of etoposide. This indicates that the reaction followed a reasonable temporal sequence to etoposide administration, and that causality is probable (Table 3).

Other factors that could have been associated with the muscle cramps in the case of this patient included cisplatin-induced electrolyte abnormalities, the anti-emetic metoclopramide, and polysorbate 80 [19-22]. However, our patient's electrolytes remained within normal ranges throughout the four cycles ruling out electrolyte abnormalities inducing muscle cramps. Metoclopramide is known to work on dopamine receptors and can cause extrapyramidal symptoms (EPS) which can manifest as muscle cramps [20]. But our patient was only

Naranjo Adverse Drug Reaction Probability Scale				
Question	**Yes**	**No**	**Do Not Know**	**Score**
1- Are there previous conclusive reports on this reaction?	+1	0	0	0
2- Did the adverse event appear after the suspected drug was administered?	+2	-1	0	2
3- Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered?	+1	0	0	1
4- Did the adverse event reappear when the drug was re-administered?	+2	-1	0	2
5- Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	2
6- Did the reaction reappear when a placebo was given?	-1	+1	0	0
7- Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8- Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9- Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10- Was the adverse event confirmed by any objective evidence?	+1	0	0	0
Total Score				7

Table 3: Naranjo Probability Scale.

administered metoclopramide on as needed basis and mostly at home rather than during his hospital stays. The last factor to rule out is the contribution of polysorbate 80 to these muscle cramps. Polysorbate 80 is a solvent used in the preparation of etoposide and has been reported as the causative agent leading to acute hypersensitivity reactions (HSR) with etoposide. These reactions manifest as dyspnea, chest discomfort, hypotension, wheezing, and flushing of face mediated by histamine release [21,22]. Our patient did not experience any of these reactions and thus HSR related to polysorbate 80 in etoposide are also ruled out.

Etoposide-induced muscle spasms have been described in some Food and Drug Administration (FDA) reports published on eHealthMe as a rare adverse effect. Among 35,151 people who developed side effects while taking etoposide, 42 experienced muscle spasms (0.12%). These spasms were most commonly seen in male, who are 10-19 years of age, have been taking the drug for less than one month, are concomitantly receiving cisplatin and have documented bone metastasis [7]. Our patient fits some of these characteristics being a 27-year-old male who has been taking BEP but has lung metastasis. Few old cases discussed etoposide-induced hypersensitivity reactions that manifested as bronchospasms and flushing [23,24]. Cisplatin-based chemotherapy was associated with acute vascular and cerebral ischemic events as recently shown in a case report [25]. However, in our case, the patient did not develop any symptoms of type 1 allergic reaction or acute coronary syndrome.

Oral baclofen is found to be effective in many patients with spasticity, regardless of the underlying disease leading to spasticity or the severity of the spasms. However, common adverse effects of oral baclofen, such as muscle weakness, nausea, somnolence and paranesthesia, affect between 25% and 75% of patients, and limit its usefulness [26]. In this case report, baclofen was not tried but diazepam was successfully used instead. Diazepam, a benzodiazepine derivative, decreases neuronal excitability by binding Gamma-Aminobutyric Acid (GABA) receptors in the limbic system, potentiating the inhibitory activities of GABA. It can be used as an adjunct therapy for convulsive disorders and relief of skeletal muscle spasms. After oral diazepam administration, more than 90% of diazepam is absorbed with an average time to reach peak plasma concentrations of 1-1.5 hours. Diazepam is hepatically metabolized by CYP3A4 and 2C19 to the active metabolites N-desmethyldiazepam and temazepam. Diazepam and its active metabolites are excreted in the urine. The elimination half-life of diazepam is up to 24 hours, and 100 hours for its active metabolite N-desmethyldiazepam [27]. Diazepam was used in the pharmacologic management of spasticity in multiple sclerosis when no clinical improvement was seen with baclofen, tizanidine and gabapentin as first-line options. The management of chemotherapy-induced muscle spasms in cancer patients is not well described in the literature. Based on the successful use of diazepam in our patient, this option warrants clinical consideration.

Conclusion

To our knowledge, this is the first case report of etoposide-associated muscle cramps that is managed with diazepam. A temporal and causal relationship of etoposide-associated muscle cramp was established using the Naranjo probability scale. Despite the rarity of the event, clinicians should be aware that muscle cramps may occur as an adverse reaction of etoposide, and diazepam may be useful as a pre-emptive measure in such cases.

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