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Case Report

Management of 5-fluorouracil Overdose with Uridine Triacetate in a Patient Unable to Tolerate Oral Administration of Antidote

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Abstract

A 55-year-old woman with a history of adenocarcinoma of the colon presented to the Emergency Department after her home infusion pump delivered a large dose of 5-fluorouracil over 35 minutes rather than the intended 46 hours. She was subsequently admitted to the hospital for supportive care, in addition to treatment with the FDA-approved antidote, uridine triacetate. She was unable to tolerate the antidote beads orally due to its bitter taste and was noted to have undigested beads in her colostomy bag. As such, a nasogastric tube was placed and the beads were crushed to improve delivery of the antidote. Implemented supportive measures included close monitoring with telemetry and neurologic evaluations, prophylaxis with fluconazole and acyclovir to prevent infection, use of filgrastim to aid in neutrophil recovery, and administration of palifermin to prevent severe mucositis. She was discharged on hospital day six after completion of the antidote and was able to resume chemotherapy 26 days following the overdose.

Uridine triacetate is an essential therapy in the management of 5-fluorouracil overdose. In the case of patients unable to tolerate swallowing the bitter medication beads, they may be crushed and delivered in a suspension through a nasogastric tube without losing efficacy.

Keywords: 5-fluorouracil; Uridine triacetate; Overdose; Colon cancer

Abbreviations

5-FU: 5-fluorouracil; NG: Nasogastric; IV: Intravenous; WBC: White Blood Cell; Ml: Milliliter; FDA: Food and Drug Administration; G-CSF: Granulocyte-Colony Stimulating Factor

Case Presentation

A 55-year old woman with adenocarcinoma of the ascending colon (stage IV) status post-colectomy four months prior presented to an outpatient chemotherapy center for cycle 14 of folinic acid, 5-fluorouracil, and oxaliplatin (a chemotherapy regimen known as FOLFOX). After infusion was completed in the chemotherapy center, a Curlin® ambulatory infusion pump was attached to the patient and set with the intention to deliver 4032 mg of 5-fluorouracil over the following 46 hours, which allowed her to return home to complete treatment. Within 35 minutes of the pump being programmed and attached, the patient's husband called to report that the pump had alarmed. Upon checking the chemotherapy bag he realized it was empty—the infusion had completed. He was instructed to bring the patient to the Emergency Department immediately.

This patient was admitted to the inpatient Cardiology floor at 4:32 pm on the day of overdose (day zero). Telemetry and scheduled neurologic evaluations were begun. The antidote, uridine triacetate, was ordered (Figure 1) for overnight shipment. On hospital day one, she was started on fluconazole, acyclovir, filgrastim, and palifermin. Nausea was managed with scheduled anti-emetics. At 12:34 pm on hospital day one the first dose of uridine triacetate was delivered. Over the course of hospital day one and into hospital day two the patient was unable to tolerate swallowing the antidote. She remarked on the bitter taste of the medication and despite mixing it in several media (apple sauce, pudding, gelatin) was unable to swallow an entire 10-gram dose. In addition, intact granules from the antidote were noted by nursing staff in her colostomy bag. Given concern that our patient was unable to swallow the antidote, a Nasogastric (NG) tube was placed on hospital day two. This allowed for the granules containing the antidote to be crushed and for our patient to avoid the bitter taste of the medication. On hospital day five the patient was noted to have an acute kidney injury (creatinine 1.4, fractional excretion of sodium 0.2%), which was successfully managed with IV fluids (Table 1). By hospital day six the full course of the antidote (20 doses) was completed and patient was discharged home in stable condition. At no point during her admission did she develop cardiac or neurologic side effects. She returned to clinic eight days following discharge and was found to be neutropenic with a white blood cell count of 2.0 k/mm3 with 330 neutrophils. She was given daily filgrastim as an outpatient and WBC count improved to 11.5 k/mm3 on follow-up. Chemotherapy was resumed 26 days following 5-fluorouracil overdose.

Discussion and Conclusion

5-fluorouracil is a fluorinated pyrimidine anti-metabolite that is used in chemotherapeutic regimens, commonly to treat colon

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Table 1: Laboratory data during hospitalization.

Hospital Day	0	1	2	3	4	5	6	Post-discharge	Post-discharge (day 18)
White blood cell count (k/mm^3)	5.6	9	16.7	13.5	17.6	17.8	11.5	2	11.5
Total neutrophils (/mm^3)	3250	7770	13933	9814	14659	15298	10191	330	5438
Hemoglobin (g/dL)	11.7	10.8	11.9	12.7	12.4	12.2	11.5	12.4	12,0
Platelet count (k/mm^3)	138	114	99	100	107	95	71	87	105k
Creatinine (mg/dL)	0.9	1	1.1	1	1.1	1.4	1.2	1.2	Not obtained.
Liver panel									Not obtained.
-Total bilirubin (mg/dL)	0.2	0.5	0.6	0.6	0.4	0.4	0.3	0.2	
-ALP (U/L)	218	197	204	198	206	201	169	257	
-GGT (U/L)	[a]…	143	149	137	132	133	131	[a]…	
-AST (U/L)	28	31	47	29	21	20	15	24	
-ALT (U/L)	30	33	51	40	35	29	24	36	

Table 2: Management of side effects secondary to 5-FU toxicity.

Side Effect	Management
Nausea	IV dexamethasone 8 mg daily IV ondansetron 8 mg every 8 hours IV prochlorperazine 10 mg every 6 hours as needed
Mucositis	Oral palifermin 60 mcg/kg every 24 hours for three doses
Bone marrow suppression	Subcutaneous filgrastim 300 mcg daily
Increased risk of infection (secondary to bone marrow suppression)	Oral fluconazole 400 mg daily Oral acyclovir 400 mg twice daily
Increased risk of cardiac arrhythmia	On-site telemetry
Risk of neurologic toxicity	Scheduled neurologic examinations

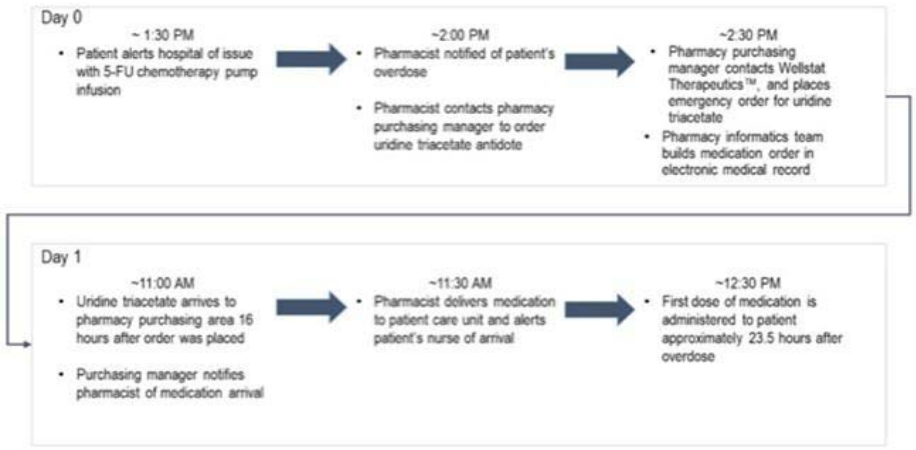

Figure 1: Represents the timeline of events that occurred in obtaining the antidote, uridine triacetate, for our patient with 5-fluorouracil overdose.

or pancreatic cancer [1]. Upon administration, it is converted into three active metabolites, all of which promote DNA or RNA damage [2,3]. After conversion to its active metabolites, 5-fluorouracil is preferentially taken up by actively dividing cells. It enters extracellular fluid, bone marrow, intestinal mucosa, and liver, as well as CSF and brain tissue [1]. Given this wide distribution it has numerous side effects at therapeutic levels; at levels of overdose it can have devastating toxicity. According to a root cause analysis performed by the Institute for Safe Medication Practices Canada, patients are at increased risk for fluorouracil toxicity if the infusion rate is at least 25% faster than the intended rate for the patient or if the given dose is greater than 10% of the intended dose [4,5]. Side effects of toxicity include mucositis with nausea, vomiting, diarrhea, GI ulceration and bleeding; neurologic changes including mental status changes, ataxia, and neuropathy; cardiac manifestations of cardiac shock and fatal arrhythmias; and bone marrow suppression with thrombocytopenia, leukopenia, and agranulocytosis [6].

Uridine triacetate (Vistoguard®)is a new drug developed by Wellstat Therapeutics that has been FDA approved since 2015 for emergency treatment of adult and pediatric patients following fluorouracil or capecitabine overdose [7,8]. It is an acetylated prodrug of uridine, and following oral administration, it is deacetylated by

nonspecific esterases present throughout the body, yielding uridine in the circulation.Uridine competitively inhibits cell damage and cell death caused by the cytotoxic metabolites of 5-FU. In addition, excess circulating uridine competes with metabolites of 5-FU for incorporation into RNA [9]. Standard management of 5-fluorouracil overdose used to involve supportive care alone.In a review by von Borstel and colleagues, of 13 patients who received supportive care alone following 5-fluorouracil overdose, 11 died. However, in clinical studies reported by Ma, a total of 137 of 142 overdose patients (96%) treated with uridine triacetate survived, a significant improvement compared to the historical cohort who received supportive treatment alone[10].

In adult patients with suspected 5-FU overdose, treatment with uridine triacetate should be initiated as soon as possible following overdose. It is dosed 10 grams (1 packet) orally every six hours for 20 doses. Each dose should be mixed with three to four ounces of soft foods and ingested within 30 minutes without regard to meals. When necessary, treatment can be given via nasogastric or gastrostomy tube [11].

After our patient's admission to the inpatient Hematology-Oncology service, our focus was two-fold: first was having the antidote ordered and shipped to our institution in a timely manner, and second was on detection, prevention, and treatment of side effects and toxicity (Table 2). Since cardiac arrhythmias can be fatal in overdose [12], our patient was placed on an inpatient cardiology unit so that she could be monitored with on-site telemetry. Scheduled neurologic evaluations (initially every two hours) were ordered due to a risk of neurologic toxicities. She was given scheduled dexamethasone and ondansetron as well as prn prochlorperazine throughout her hospitalization for nausea and vomiting associated with overdose. Palifermin was given orally every 24 hours for three doses to reduce the risk of mucositis. As bone marrow suppression is a possibility even at standard doses of 5-fluorouracil, she was started on fluconazole and acyclovir for infection prophylaxis as well as filgrastim to aide in neutrophil recovery. These medications were given throughout her hospital stay. Despite a tentative plan to start ciprofloxacin if her neutrophil count dropped below 1000 while hospitalized, this did not occur during her admission. She did become neutropenic as an outpatient and filgrastim was restarted, but she never required admission or treatment for febrile neutropenia.

To our knowledge, this is the first case report in the literature describing administration of uridine triacetate via NG tube. In one clinical trial, 14 patients were administered uridine triacetate via NG or gastric tube without any compromise in clinical efficacy or safety [10]. Given the successful outcomes observed in that clinical trial the manufacturer has approved NG or gastric tube administration of uridine triacetate [9]. Additional information was obtained from the manufacturer to ensure safe and effective NG tube administration in our patient. This information was provided by pharmacy to nursing as part of the medication order administration instructions in the electronic medical record. For each dose of medication, the full contents of a 10-gram packet of uridine triacetate granules were crushed until a fine powder was formed. Per the manufacturer, it is important that the granules are ground into a very fine powder to prevent obstruction of the NG tube. This powder was then mixed with 100 mL of a reconstituted suspension of thickening agent (Simply Thick®) and water. This reconstituted suspension of uridine triacetate was then administered via NG tube. After administration, the NG tube was flushed with water to prevent clogging and to ensure the full dose of medication was administered. The manufacturer recommends use of the thickening agent in order to form a stable suspension of uridine triacetate. If a thickening agent is not used, uridine triacetate will not form a stable suspension and should be administered immediately after mixing. Uridine triacetate is not a hazardous medication and there are no special handling instructions to consider when crushing granules. If a patient is able to take oral administration of uridine triacetate it is important they be instructed to avoid chewing the medication granules due to the bitter taste of the drug which may contribute to potential nausea and/or vomiting.

In summary, uridine triacetate is essential for management of 5-fluorouracil overdose and is now FDA approved for this use. It appears that this is the first case reported in the literature since FDA approval. In certain settings, such as a patient being unable to tolerate oral medication or if there are concerns about poor oral absorption given history of colectomy, it may be appropriate to crush the granules and deliver through a nasogastric tube to improve tolerability and absorption. Close detail must also be paid to symptom management and providing supportive and preventive care with use of anti-emetics, G-CSF, and infection and mucositis prophylaxis.

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