Fluorouracil-induced Hyperammonemia in a Patient with Colorectal Cancer

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Abstract. *Fluorouracil (5-FU; Adrucil®) is a pyrimidine analog antineoplastic chemotherapy agent which works by interfering with DNA and RNA synthesis. It has an uncommon toxicity called hyperammonemic encephalopathy. This neurotoxicity is associated with a high-dose administration of 5-FU (2,600 mg/m^2/week), with an incidence rate of 5.7%, and is not normally seen with the current dose of 1,200 mg/m^2 infused over 46 h. The mechanism behind this neurotoxicity is not known but is possibly due to accumulation of fluorocitrate, a byproduct of 5-FU metabolism. This by-product inhibits the Krebs cycle, which causes impairment of the adenosine triphosphate-dependent urea cycle. By impairing this cycle, ammonia is not converted to urea, which in turn this leads to an accumulation of ammonia. The accumulated ammonia in the brain is metabolized to glutamine, which has been suggested to cause an increase in intracranial pressure and cerebral edema. This case report discusses how a 40-year-old male with colorectal cancer experienced 5FU-induced hyperammonemia and was treated for it and how reducing the dose by 50% led to resolution of this symptom from reoccurring.*

Fluorouracil (5-FU; Adrucil®) is a pyrimidine analog antineoplastic chemotherapy agent which works by interfering with DNA and RNA synthesis (1). It is generally used in combination treatment with other medications for various cancer types such as colonic, rectal, breast, head and neck, gastrointestinal tumors and some topes of skin cancer (2). 5-FU is typically given as an intravenous injection or infusion. Common side-effects experienced by patients include diarrhea, nausea and vomiting, mouth sores, sensitivity to light, and a metallic taste in the mouth. It is also associated with an uncommon toxicity, called hyperammonemic encephalopathy. This neurotoxicity is associated with the high-dose administration of 5-FU (2,600 mg/m^2/week), with an incidence rate of 5.7%, and is not normally seen with the current dose of 1200 mg/m^2 infused over 46 hours (3). 5-FU-induced encephalopathy is characterized by a sudden alteration in mental status, lactic acidosis, and respiratory alkalosis associated with elevated plasma level of ammonia (4). Onset of toxicity varies, ranging from 0.5 to 5 days following the initiation of 5-FU (5).

The mechanism behind this neurotoxicity is not known, Koenig and Patel suggested that it is possibly due to the accumulation of the by-product of 5-FU metabolism called fluorocitrate. This by-product inhibits the Krebs cycle, which causes impairment of the adenosine triphosphate-dependent urea cycle. By impairing this cycle, ammonia is not converted to urea, which in turn this leads to an accumulation of ammonia (6). The accumulated ammonia in the brain is metabolized to glutamine, which has been suggested to cause an increase in intracranial pressure and cerebral edema (6, 7). Another proposed mechanism of this neurotoxicity is linked to dihydropyrimidine dehydrogenase deficiency (3); however, this mechanism does not explain patients who did not experience this neurotoxicity during their first exposure to 5-FU, patients with such deficiency should present with encephalopathy on their first exposure to 5-FU without elevation of their ammonia level (8). This suggests that hyperammonemia seen in these patients is most likely secondary to 5-FU administration. Reducing the 5-FU dose or switching to capecitabine, an oral pro-drug of 5-FU, has been shown to prevent reoccurrence of hyperammonemic encephalopathy; however, capecitabine-induced neurotoxicity has been reported in 0.1 to 0.5% of patients (2).

This report describes the case of a patient who exhibited symptoms of 5-FU-induced hyperammonemic encephalopathy without re-occurrence of symptoms upon reduction of the 5-FU dose by 50%.

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Case Report

A 40-year-old male with a history of chronic kidney failure, with a stable creatinine baseline of around 1.5 mg/dl, started showing polycythemia on his blood counts with eventual bleeding per the rectum, which led to colonoscopy. Upon results of the colonoscopy, the diagnosis of colonic cancer and staging soon followed. The patient was found to have metastases to the liver, as well as the pelvic bone. A few months following the diagnosis, he underwent colonic resection and was started on adjuvant chemotherapy. The patient was started on FOLFIRI plus Avastin. The standard regimen consists of irinotecan *i.v.* at 180 mg/m^2 over 90 min on day 1; leucovorin *i.v.* at 400 mg/m^2 over 2 h on day 1; fluorouracil *i.v.* bolus at 400 mg/m^2 on day 1 followed by 2,400 mg/m^2 continuous *i.v.* infusion over 46 h beginning on day 1; cycle repeated every 14 days until disease progression or unacceptable toxicity and Avastin *i.v.* at 7.5 mg/kg every 3 weeks.

Following the first two cycles, the patient presented with intractable nausea and vomiting after completion of chemotherapy sessions, but after three to four days of the nausea and vomiting his symptoms usually improved. On the third cycle, he did not experience the same results. The day after the patient underwent his third round of chemotherapy with FOLFIRI and Avastin, he presented to the emergency room (ER) with altered mental status. At home, by mid-afternoon his wife had noticed he was slowly starting to become more obtunded and lethargic than he had been in the morning or after previous chemotherapy, hence prompting his wife to bring him to the ER. In the ER, he was barely responsive, although his eyes were open, but his gaze did not track. He was also retching intermittently. He had vomited yellowish-colored fluid multiple times since the chemotherapy. He also had a small brown semi-liquid bowel movement whilst in the ER. He had not complained of any pain earlier when he had been more alert. He had no shortness of breath, chest pain, fever, rigors or chills. He had not had any such presentation after his previous two chemotherapy sessions, except for the moderate somnolence due to an antiemetic dose of lorazepam (Ativan) after those episodes, but this time he had not taken any Ativan and his mental status was much worse. No seizure-like activity was noted and no falls were reported. Patient himself was unable to provide any history due to his mental state and all history was obtained from his wife and other family members. The patient was not known to have drug allergies and there was no history of smoking, alcohol or illicit drug use.

Upon physical examination, the patient's eyes were open, but did roll upwards. He did have rolling eye movements but without any gaze preference. He spontaneously moved all four extremities and retched intermittently, but apart from that, he did not respond to painful stimuli or any other verbal instructions. The patient was intubated for airway protection.

His most recent vital signs at the time were blood pressure of 130/70 mmHg, oxygenating 99% on room air, respiratory rate of 22, heart rate of 90 bpm and temperature of 98.4˚F. His chest was clear to auscitation with slightly increased effort. The patient's heart rate was slightly tachycardic with regular rhythm. The complete blood complete blood count (CBC) showed an elevated white blood cell count of 21,000/μl (normal range: 5,200-12,400/μl) with blood and urine negative for infection. The remainder of the CBC values were within normal limits. Some of his panel results were as follows: sodium 151 mEq/l (normal range: 135-146 mEq/l), potassium was normal, calcium 10.3 mg/dl (8.6-10 mg/dl), blood urea nitrogen 48 mmol/l (normal range: 9-23 mmol/l), creatinine 2.5 mg/dl (normal range: 0.7-1.1 mg/dl). Arterial blood gas levels were abnormal, the pH was 7.08 mol/L, and pCO_2 was 29 mmHg, bicarbonate was less than 10 mmol/, pO_2 was 250 mmHg. Liver function tests were as follows: aspartate aminotransferase 49 IU/I (normal range: 10-49 IU/I); alanine transaminase 82 IU/I (normal range: 0-33 IU/I); alkaline phosphatase 269 IU/I (normal range: 45-129 IU/I). The shocking value was the elevated ammonia level which upon arrival at the ER was 611.1 mmol/l (normal range: 11-35 mmol/l). His lactic acid level was 12.2 mg/dl (normal range: 4.5 to 19.8 mg/dl), phosphorus 10.1 mmol/l (normal range: 2.4-5.1 mmol/l) and uric acid was 14 mmol/l (normal range: 3-7 mmol/l).

The patient was admitted in order to rule out tumor lysis syndrome. Upon patient presentation, physicians were perplexed as to the potential diagnoses. Some of the ideas initially proposed included liver failure, tumor lysis syndrome or even a combination of both.

At presentation, the patient was started on hemodialysis to potentially help with the metabolic acidosis and hyperammonemia. Meanwhile, supportive care was started in the hope that it was an acute process which was somehow precipitated by his chemotherapy. The patient was kept on a ventilator while he battled acute encephalopathy and severe metabolic derangements.

After hydration, the patient's ammonia level was 611.1 mmol/l, dropping to 515 mmol/l within several hours of presentation then to 59.9 mmol/l by the next day. Moreover, the lactic acid level started to drop by the following day. This prompted the addition of lactulose, and after two days, the patient's ammonia level had dropped to 28.4 μmol/l, returning to within the normal range. The patient was alert and oriented at this point, which was 3 days after the 5-FU dose, and was discharged from the hospital on the fourth day.

The patient reported to the oncologist for follow-up and his 5-FU dose was reduced by 50% a week later when he underwent the second cycle and he did not experience hyperammonemia induced by 5-FU again.

Discussion

Hyperammonemia is a rare adverse effect of 5-FU therapy but can be very serious, even fatal, when it does actually occur in patients. If it is recognized early on and treated correctly, then the patient can return to normal very quickly. In our case, the patient and caregivers recognized something was wrong very quickly. Initially, we treated the hyperammonemia but did not know its cause and only after some research saw hyperammonemia as being a rare side-effect of 5-FU. Several other case reports had reported that reducing the 5-FU dose by 50% or using capecitabine were reasonable alternatives for such cases. Reducing the 5-FU dose by 50% was effective for our patient for the subsequent cycle.

Case reports such as these can make physicians more aware of what to do in such cases. Pharmacists, physicians and nurses can play a significant role in educating patients receiving 5-FU about all possible side-effects and when they should go to the emergency room. Currently the best for resolving hyperammonemia as a result of 5-FU is to reduce the dose by 50% or switch therapy to capecitabine.

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Conflicts of Interest

None.

References

1 Matuo R and Henriques J: 5-Fluorouracil and its active metabolite FdUMP cause DNA damage in human SW620 colon adenocarcinoma cell line. J Appl Toxicol *29(4)*: 308-316, 2009.
2 Advani P and Fakih M: 5-FU-induced hyperammonemic encephalopathy in a case of metastatic rectal adenocarcinoid successfully rechallenged with the fluoropyrimidine analog, capecitabine. Anticancer Res *31(1)*: 335-338, 2011.
3 Yeh K and Cheng A: High-dose 5-fluorouracil infusional therapy is associated with hyperammonemia, lactic acidosis and encephalopathy. Br J Cancer *75(3)*: 464-465, 1997.
4 Espinós J and Nieto Y: Idiopathic hyperammonemia following high-dose chemotherapy. Bone Marrow Transplant *37(9)*: 899, 2006.
5 Liaw C and Yeh C: Risk of hyperammonemic encephalopathy in cancer patients who received continuous infusion of 5-fluorouracil with the complication of dehydration and infection. Anticancer Drugs *10(3)*: 275-281, 1999.
6 Ig H and Patel A: Biochemical basis for fluorouracil neurotoxicity. The role of Krebs cycle inhibition by fluoroacetate. Arch Neurol *23(2)*: 155-160, 1970.
7 Nott L and Fletcher J: Hyperammonemia encephalopathy: An important cause of neurological deterioration following chemotherapy. Leuk Lymphoma *48(9)*: 1702-1711, 2007.
8 Yeh K and Cheng A: 5-Fluorouracil-related encephalopathy: at least two distinct pathogenetic mechanisms exist - reply. Br J Cancer *77(10)*: 1711-1712, 1998.

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