CASE REPORT

Subtherapeutic posaconazole prophylaxis in a gastric bypass patient following hematopoietic stem cell transplantation

Emily A. Highsmith, PharmD, BCCCP,
Department of Pharmacy, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Vi P. Doan, PharmD, BCOP,
Department of Pharmacy, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Todd W. Canada, PharmD, BCNSP, BCCCP, FASHP, FTSHP, FASPEN,
Department of Pharmacy, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Purpose. A case of invasive fungal infections (IFIs) with subtherapeutic posaconazole prophylaxis in a gastric bypass patient following hematopoietic stem cell transplantation (HSCT) is reported.

Summary. A 52-year-old malnourished male with a medical history of Roux-en-Y gastric bypass for obesity developed acute myelogenous leukemia and underwent allogeneic HSCT approximately 17 months later. He was admitted 1 month after HSCT for failure to thrive and initiated on parenteral nutrition due to worsening diarrhea and suspected gastrointestinal graft-versus-host disease (GI GVHD). During admission, the patient was continued on daily oral posaconazole for antifungal prophylaxis and was found to have subtherapeutic posaconazole and deficient vitamin levels, likely secondary to his gastrojejunostomy and increased gastric transit time. The oral posaconazole was altered to twice-daily dosing in an effort to increase serum drug levels and prevent IFIs.

Conclusion. Patients with a history of gastric bypass are at increased risk for malabsorption of oral posaconazole and nutrients, especially following HSCT with suspected GI GVHD.

Keywords: gastric bypass, hematopoietic stem cell transplantation, intestinal absorption, posaconazole

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Bariatric surgeries such as gastric bypass procedures are increasingly common elective procedures. In 2018, the American Society for Metabolic and Bariatric Surgeries estimated that 252,000 bariatric surgeries were performed, representing a 40% increase over a 5-year period.[1] As obesity rates continue to rise, procedures such as Roux-en-Y gastric bypass (RYGB) or gastric sleeve will increase in prevalence.

Hematopoietic stem cell transplantation (HSCT) is considered to be a curative therapy for a variety of malignancies, including leukemias, myelomas, and lymphomas. Over the past 6 decades, HSCT has dramatically increased in prevalence. In 2015, over 21,000 transplantations were performed, and this number is expected to increase.[2] Following allogeneic HSCT, patients require long-term immunosuppression for prevention of graft-versus-host disease (GVHD), as well as prophylaxis for *Pneumocystis jiroveci* pneumonia, invasive fungal infections (IFIs), and viral infections.

Previous literature has established perioperative management for bariatric procedures including nutritional management, as well as evaluation of vitamins and serum trace element levels.[3] Unfortunately, the published guidance for oral medication absorption following RYGB or ways to ameliorate decreased absorption is scarce.[4]

We describe a patient who was formerly obese before RYGB who developed acute myelogenous leukemia and underwent HSCT with subtherapeutic serum posaconazole levels during use of oral tablets and nutrient malabsorption with severe malnutrition.

Address correspondence to Dr. Highsmith (ehighsmith93@gmail.com).

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Case report

A 52-year-old malnourished male was hospitalized for significant generalized weakness, fatigue, and failure to thrive. His medical history was significant for positivity for hepatitis B core antibody and obesity with a body mass index of 53.3 kg/m^2, and he underwent RYGB in May 2018. Before RYGB, the patient reported his weight to be 165 kg with a weight loss of approximately 100 kg over the course of a year. He was diagnosed with acute myelogenous leukemia in April 2019, for which he underwent allogeneic HSCT with cells from a matched sibling in October 2019. Before initiation of the HSCT conditioning regimen and throughout his admission in October 2019, he experienced minimal appetite and increased vomiting and diarrhea and continued to lose weight. He was enrolled on a protocol where he received a myeloablative intensity conditioning regimen that consisted of busulfan (area under the curve target of 6,000), fludarabine, aldesleukin, and natural killer cells on day –8 before stem cell infusion. His GVHD prophylaxis regimen included posttransplant administration of cyclophosphamide on days 3 and 4, followed by administration of tacrolimus starting on day 5. He received posaconazole 300 mg intravenously (IV) daily for 14 days as IFI prophylaxis per our institution's standard of care. The patient was partially engrafted 19 days following HSCT but remained anemic and thrombocytopenic (Table 1). His posaconazole dose was switched to 300 mg of the oral tablets (three 100-mg tablets) daily for 20 days following HSCT. His hospital course was complicated by *Burkholderia cepacia* septicemia requiring admission to the intensive care unit and treatment with subsequent discharge on post-HSCT day 28. Two days after discharge, the patient experienced significant generalized weakness, fatigue, dizziness, and hypothermia accompanied by rigors and was readmitted to the hospital. Upon readmission, the patient's weight was 53 kg and significant muscle and temporal wasting was evident. He continued to receive posaconazole 300 mg orally daily.

KEY POINTS

- Patients with altered gastric anatomy may be at risk for malabsorption of drugs and nutrients.
- Patients with gastrointestinal graft vs host disease (GVHD) or increased gastric transit time are at increased risk for altered intestinal absorption.
- The use of therapeutic drug monitoring may help guide clinicians to optimal dosing regimens in patients exhibiting malabsorption or altered clearance.

His hospital course was significant for a large volume (>1 L/day) of watery diarrhea while receiving an oral diet, which was concerning given that this can indicate gastrointestinal infection or GVHD (GI GVHD). The patient tested positive for *Clostridioides difficile* DNA and negative for *C. difficile* toxin, and the transplant team treated him with vancomycin 125 mg orally 4 times daily to suppress colonization and prevent an active infection. The rest of the patient's GI multiplex panel was negative for pathogens. Because of profound thrombocytopenia (Table 1), high risk for bleeding, and patient refusal, a feeding tube was not initially placed. Parenteral nutrition (PN) was initiated on hospital day 5 for failure to thrive and suspected GI GVHD via endoscopy and sigmoidoscopy performed the same day. The patient's tissue biopsies were negative for GI GVHD with the transplant team empirically treating the patient with an 8-day course of tapering methylprednisolone administered IV. Repeat endoscopy and sigmoidoscopy were performed in December 2019, and tissue biopsies were again negative for GI GVHD. PN was discontinued 5 days after placement of an enteral feeding tube, and the patient was started on continuous enteral feeding due to chronic poor oral intake.

Given the suspicion of GI GVHD, malabsorption with a history of RYGB, and risk for fungal infection with concomitant use of corticosteroids, serum posaconazole trough levels were obtained to assess oral absorption.

Table 1. Select Laboratory Values on Readmission

Analyte	Value	Reference Range[a]
White blood cell count, /μL	7,400	4,000-11,000
Red blood cell count, ×10^6/μL	2.72	4.5-6
Hemoglobin, g/dL	7.9	14-18
Hematocrit, %	23.1	40-54
Mean corpuscular volume, fL	85	82-98
Platelet count, ×10^3/μL	18	140-440
Blood urea nitrogen, mg/dL	48	6-23
Serum creatinine, mg/dL	1.01	0.67-1.17
Alanine aminotransferase, U/L	14	≤41
Aspartate aminotransferase, U/L	21	≤40
Total bilirubin, mg/dL	0.5	<1.2
Albumin, g/dL	3.2	3.5-5.2

[a]Reference values are institution specific.

The posaconazole assay measured total drug concentration as opposed to the concentration of available free drug. Figure 1 illustrates the patient's posaconazole trough levels, all of which were subtherapeutic (<700 ng/mL) on an oral tablet dosage, despite initial intravenous dosing of 300 mg daily followed by 300 mg orally daily (during his prior hospitalization). As depicted in Figure 1, following multiple instances of subtherapeutic trough levels, the patient was transitioned to a dosing strategy with posaconazole 300 mg administered twice daily without achieving a posaconazole level of >700 ng/mL (Table 2). He was also initiated on bridge therapy with caspofungin that was intended to continue until posaconazole levels were therapeutic. The patient's heart rate–corrected QT interval (QTc) was also closely monitored over the course of treatment and was unaffected by the increased dose of posaconazole (Table 3).

During this admission, the patient remained on oral tacrolimus capsules for prevention of GVHD (Table 2) without evidence of malabsorption, as his serum tacrolimus levels remained therapeutic (desired goal of 7–12 ng/mL) with only minor dosage adjustments. Because the patient's altered gastric anatomy resulted in rapid gastric transit and diarrhea on an oral diet, it is unlikely that the patient was appropriately absorbing all medications. We suspected absorption issues with other oral medications, such as valacyclovir, letermovir, and entecavir, but were unable to measure serum levels of these agents. Fortunately, the patient did not develop infections related to the organisms for which these medications provide prophylaxis, which may support adequate absorption despite the RYGB procedure. In addition to receiving immunosuppression and anti-infective agents, the patient remained on pantoprazole during the course of his admission.

Before initiating PN, a variety of nutrient levels were assessed (Table 4) with notable hyperhomocysteinemia and folate and free retinol (vitamin A) levels consistent with deficiencies from RYGB-related malabsorption and poor oral intake. Surprisingly, not all nutrient levels were abnormal and vitamin B_{12} levels were notably elevated, which may be attributed to an oral vitamin supplement the patient reported taking before admission. We were unable to obtain the constituents of the vitamin supplement because the patient did not have it at the time of admission.

The patient was subsequently discharged to inpatient rehabilitation on hospital day 39 and was discharged from rehabilitation on hospital day 51. He unfortunately died 1 month after discharge due to severe malnutrition and multiple-system organ failure.

Discussion

Posaconazole is a second-generation triazole medication commonly used for prophylaxis and treatment of IFIs. It is a potent cytochrome P-450 isozyme 3A4 (CYP3A4) inhibitor and prolongs the QT interval, requiring careful monitoring when taken subsequently to CYP3A4 substrates or other QT interval–prolonging medications. Commercially available formulations include an oral suspension, a delayed-release tablet, and an intravenous formulation.[5] Posaconazole has widely varying oral bioavailability, ranging from 8% to 47%. Factors that may enhance the bioavailability of posaconazole include administration with a high-fat meal, low gastric pH, and absence of diarrhea or mucositis.[6,7] Furthermore, posaconazole's formulation impacts its bioavailability. The oral suspension has been shown to have significantly lower bioavailability when administered without food or in the setting of acid-reducing agents.[8,9] In contrast, the delayed-release tablet has better absorption in both fed and fasted conditions.[9] Other risk factors for subtherapeutic posaconazole levels include diarrhea and concomitant use of a proton pump inhibitor.[10] In a prior study in which 63% and 14% of patients received a proton pump inhibitor and histamine H_2 receptor antagonist, respectively, only 18%

Figure 1. Posaconazole level monitoring and dosing strategies. PO indicates orally; BID, twice daily.

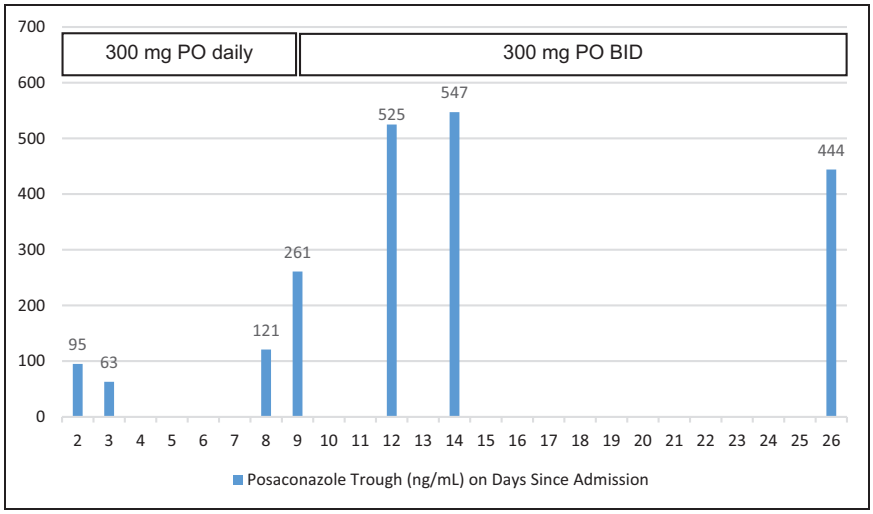

Table 2. Select Medications During Readmission

Time Interval	Medication
Day 1–discharge	Entecavir 0.5 mg orally daily
Day 1–discharge	Letermovir 480 mg orally daily
Day 1–discharge	Valacyclovir 500 mg orally twice daily
Day 2–discharge	Pantoprazole 40 mg orally twice daily
Day 1–day 8	Posaconazole 300 mg orally daily
Day 9–discharge	Posaconazole 300 mg orally twice daily
Day 9–discharge	Caspofungin 50 mg IV daily
Day 1–day 18	Tacrolimus 1 mg orally every morning; 0.5 mg orally every evening
Day 19–day 26	Tacrolimus 1 mg orally twice daily
Day 26–discharge	Tacrolimus 1 mg orally every morning; 0.5 mg orally every evening

Abbreviation: IV, intravenously.

Table 3. QTc Values During Patient's Hospital Stay

Day After Admission	QT Interval, ms
Day 11	488
Day 12	428
Day 19	407

Table 4. Nutrient Levels Before Initiation of Parenteral Nutrition

Analyte	Value	Reference Range[a]
Folate, ng/mL	<2[b]	4.8-24.4
Homocysteine, mg/L	7.0[b]	≤2
Vitamin B_{12}, pg/mL	3,740[b]	211-946
Methylmalonic acid, nmol/mL	0.17	≤0.40
Free retinol (vitamin A), µg/dL	17.5[b]	32.5-78
Vitamin D (25-OH), ng/mL	41	30-100
Ceruloplasmin, mg/dL	22.8	19-31
Copper, µg/dL	104	75-145
Zinc, µg/dL	91	66-110
Albumin, g/dL	3.2	3.5-5.2
C-reactive protein, mg/L	7.37	<1

[a]Reference ranges are institution specific.
[b]Abnormal result.

of patients concomitantly receiving posaconazole had a serum level below 700 ng/mL, despite the acid reduction.[11]

Posaconazole is also highly protein bound (up to 98%) and predominantly binds to albumin. Given this, it is plausible that low serum albumin levels may result in an increased fraction of unbound drug. Because only the unbound drug is able to undergo metabolism, previous case reports have hypothesized that hypoalbuminemia may result in enhanced drug clearance, which would be reflected in total drug concentrations. Until there is an assay to measure free drug, it is difficult to ascertain whether the concentration of unbound drug is able to provide sufficient antifungal coverage to prevent IFIs.[12]

Data from previous trials suggest that posaconazole trough levels of >700 ng/mL are adequate for IFI prophylaxis.[8] Others have shown that 18% to 29% of patients receiving oral posaconazole do not achieve these levels but do not appear to develop breakthrough infections.[11,13] Delayed-release tablets are the preferred oral formulation, and patients showed an increase in median trough level from 750 ng/mL to 1,090 ng/mL following a transition from the oral suspension to tablets.[8]

Previous studies have shown decreased posaconazole levels following RYGB. Increased gastric pH from a reduced number of acid-secreting parietal cells affects the solubility of posaconazole, while the restricted gastric pouch and decreased gastric residence time reduce medication absorption.[13] One study measured area under the curve before and after RYGB in healthy volunteers and found a 42% reduction in drug level following the procedure.[13] When RYGB is paired with diarrhea or damaged gastric mucosa, it is likely that drug levels are even further reduced.

GI GVHD has been associated with protein loss, diarrhea, and malabsorption. Inflammatory processes resulting from myeloablative intensity conditioning regimens and alloreactive donor T cells result in damaged small intestine mucosa.[14-16] Impaired mucosal absorption and increased gastric transit time may result in nutrient and drug malabsorption. We contacted the manufacturer of posaconazole for information regarding this patient's

management; however, there have been no studies published on subtherapeutic posaconazole levels in patients with possible GI GVHD and a history of gastric bypass (Kamien J, Merck, personal communication, November 15, 2019).

Conclusion

Patients with a history of RYGB are at an increased risk of malabsorption, and their risk may increase with worsening diarrhea, especially after HSCT. Medications such as posaconazole that exhibit variable bioavailability may have altered absorption as in the case presented here. In addition to malabsorption, altered clearance may play a role in subtherapeutic levels. Assessing trough drug levels and adjusting dosing strategies are required in these unique patient populations.

Disclosures

The authors have declared no potential conflicts of interest.

Previous affiliations

At the time of writing, Dr. Highsmith was employed by Houston Methodist Hospital.

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