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Case report

Systemic absorption of oral vancomycin in a peripheral blood stem cell transplant patient with severe graft-versus-host disease of the gastrointestinal tract

J.M. Pogue, D.D. DePestel, D.R. Kaul, Y. Khaled, D.G. Frame. Systemic absorption of oral vancomycin in a peripheral blood stem cell transplant patient with severe graft-versus-host disease of the gastrointestinal tract.
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Abstract: Oral vancomycin is often considered the drug of choice for severe *Clostridium difficile*-associated disease due to both its efficacy and pharmacokinetics. The potential for absorption is not well described in patients with impaired gastrointestinal (GI) mucosa. We describe a case of significant and potentially toxic absorption of oral vancomycin in a peripheral blood stem cell transplant patient with grade IV graft-versus-host disease (GVHD) of the GI tract. In patients with GI GVHD clinicians need to be aware of the potential for oral absorption and, in select cases, monitoring of levels may be appropriate.

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Key words: *Clostridium difficile*; CDAD; vancomycin; GVHD; graft-versus-host disease; peripheral blood stem cell transplant

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Oral vancomycin is a routinely used agent for the treatment of *Clostridium difficile*-associated diarrhea (CDAD). National experts recommend oral vancomycin for severe CDAD based on selected literature that supports an increase in efficacy over metronidazole (1) and the fact that the drug reaches concentrations $\geq$ 1000 times the minimum inhibitory concentration of the organism at the site of action without significant systemic absorption (2). These recommendations and the emergence of the more virulent, NAP-1 strain have led to a more widespread use of oral vancomycin in patient populations where both efficacy and the potential for systemic absorption have not been well studied. We report a case of significant and potentially toxic absorption of oral vancomycin in a peripheral blood stem cell transplant (PBSCT) recipient with severe gastrointestinal (GI) graft-versus-host disease (GVHD).

Case report

A 62-year-old male with myelodysplastic syndrome underwent a 10/10 HLA-matched unrelated donor PBSCT that was complicated by grade I acute GI GVHD, cytomegalovi-

rus reactivation, and human herpesvirus-6 encephalopathy. On day + 200 after transplant, he was readmitted with 4–6 episodes of diarrhea daily (average stool output 1.5–2 L/day) and he was found to have *C. difficile*, as well as grade IV GI GVHD. The computed tomography findings demonstrated congestion in the mucosa throughout the colon and the histopathologic findings were most consistent with severe (grade IV) GVHD.

However, the patient had several risk factors for *C. difficile*, including recent antibiotic use, acid suppression therapy, recent prolonged hospitalization, advanced age, and severe underlying illness due to GVHD and immunosuppression. The white blood cell count was within the normal range and pseudomembranes were not present on endoscopy; nevertheless, the diagnosis of *C. difficile colitis* was made on the basis of clinical findings in conjunction with a positive stool toxin assay (ProSpecT® *C. difficile* toxin Toxin A/B Microplate Assay; Remel Inc., Lenexa, Kansas, USA). Oral vancomycin 250 mg solution was initiated every 6 h along with rifaximin 200 mg 3 times a day for presumed severe CDAD while methylprednisolone 2 mg/kg/day intravenously was started for GVHD. Throughout the patient's course he also received 5 days of mycophenolate, 17 days of cyclosporine, 13 days of oral budesonide, and 4 days of sirolimus. The patient did not receive intravenous vancomycin during his hospitalization.

The patient's serum creatinine began to increase on hospital day 19 and, as a result, a vancomycin level was ordered and found to be 26.4 mg/L. The vancomycin was held for the next 4 days, while rifaximin was continued, with a subsequent return to the patient's baseline renal function (serum creatinine 1.5 mg/dL) and a corresponding decrease in vancomycin concentration (5.9 mg/L). Table 1 displays his vancomycin doses and levels, as well as his serum creatinine levels.

On hospital day 25, oral vancomycin was restarted at a reduced dose of 125 mg every 6 h. On day 28 of hospitalization, the vancomycin dose was again increased to 250 mg every 6 h because the patient was still having severe diarrhea. Six days after the dosage increase, a second rise in serum creatinine was observed with a corresponding vancomycin level of 13.3 mg/L. The patient went on to develop bacteremia with vancomycin-resistant *Enterococcus faecium* and *Candida glabrata*, and he died on hospital day 35.

Vancomycin concentrations in serum

Hospital day	Oral vancomycin dose (mg p.o. q6h)	Level (mg/L)	Serum creatinine	*Clostridium difficile* toxins
1	N/A	N/A	1.5	+
4–17	250	N/A	1.0–1.5	N/A
18	250	N/A	1.3	+
19	250	N/A	1.7	N/A
20	Held	C(1) = 26.4 C(tr) = 24	2.1	N/A
21	Held	22.1, 22.6	2.0	N/A
22	Held	15.1	1.8	N/A
23	Held	N/A	1.6	N/A
24	Held	8.6	1.5	N/A
25	125[1]	5.9	1.4	N/A
26	125[1]	N/A	1.3	N/A
27	125[1]	5.0	1.4	N/A
28	250[1]	4.4	1.4	N/A
29	250[2]	N/A	1.5	N/A
30	250[3]	3.7	1.5	N/A
31–33	250	N/A	1.5–2.2	N/A
34	Held	13.3	2.6	N/A
35	Held	16.3	2.8 – patient died	N/A

[1]Patient received 2 doses of vancomycin.
[2]Patient received 1 dose of vancomycin.
[3]Patient received 3 doses of vancomycin.
C(1), concentration at 1 h after oral dose; C(tr), trough concentration; N/A, not available.

Table 1

Discussion

Case reports (Table 2) describe the significant accumulation of oral vancomycin in selected patients with renal insufficiency (3–7), and a more recent case report (8) showed significant systemic vancomycin levels in a patient with severe *C. difficile* disease with normal renal function. The package insert for Vancocin® pulvules (Eli Lilly, Indianapolis, Indiana, USA) states that 'significant absorption may infrequently occur in patients with *C. difficile*-induced pseudomembranous colitis, and, in the presence of renal impairment, the possibility of accumulation exists' (2). However, systemic absorption of oral vancomycin has not been reported to our knowledge in a patient with severe GI GVHD.

We present a case of significant oral vancomycin absorption in a PBSCT patient with severe GI GVHD. Based on the timing of the vancomycin levels and patient's underlying illness, it is difficult to ascertain whether high levels of vancomycin led to renal insufficiency, or if it was the impaired renal function that led to the accumulation of vancomycin. Regardless of the exact mechanism, this patient had both clinically relevant and potentially toxic vancomycin con-

Literature review of systemic absorption of orally administered vancomycin

Number of patients	Age (years) Sex	Oral vancomycin dose (mg p.o. q6h)	Serum creatinine	Level (mg/L)	References
1	62 M	500	HD	11.3–20.3	(3)
1	32 M	250	HD	5.8	(4)
1	45 M	250	HD	2.6	(4)
1	45 M	500	HD	11–13	(4)
1	45 M	125	HD	3.4	(4)
1	28 M	500	HD	0.7–9.8	(4)
10	14–81 M/F	125	Ranged from normal to severe impairment	4/11 patients with detectable (1.0–3.1) levels	(5)
10	N/A	500	N/A	1 patient with level of 3.9, all others ≤ 1	(6)
12	N/A	500	Normal	8 had undetectable levels	(7)
	54 F	500	Normal	2.4	(7)
	89 M	500	2.3	1.2	(7)
	71 M	500	1.2	1.3	(7)
	66 F	500	HD	5.1	(7)
1	77 F	125–500 + vancomycin enemas	1.0	6.3–7.9	(8)

HD, patient on hemodialysis.

Table 2

centrations, despite never receiving intravenous vancomycin. These data are particularly interesting in the light of 2 recent reports showing patients having systemic hypersensitivity-type adverse drug reactions attributed to oral vancomycin therapy (10, 11).

The diagnosis of CDAD and response to treatment can be challenging in this patient population. GI GVHD is common and is graded based on daily stool volume with grade I disease defined as stool output >500 mL/day, grade II as >1000 mL/day, grade III as >1500 mL/day, and grade IV as >2000 mL/day (12). Symptoms of GVHD and CDAD both often include fever and leukocytosis. Because the symptoms are similar, it is often difficult to ascertain the severity of the CDAD infection versus the GVHD. Given these diagnostic limitations, empirical treatment for severe CDAD with oral vancomycin is not uncommon in the setting of GI GVHD. As demonstrated in this report, loss of GI integrity may lead to increased bioavailability, and therefore, the potential for significant accumulation of vancomycin, and possible adverse effects. The additive nephrotoxicity based on drug interactions with other medications often co-administered for transplant, such as calcineurin inhibitors, sirolimus, and foscarnet, among others, would be of additional concern. Our patient was on multiple concomitant nephrotoxins. While the concentration of these agents was not considered toxic (sirolimus levels were undetectable and cyclosporine levels remained <100 ng/mL), additive toxicity with vancomycin cannot be ruled out.

We are not able to ascertain the relative contribution of CDAD or GI GVHD to the absorption of vancomycin, but the fact that the systemic level was high after 19 days of treatment (a time course during which most patients with CDAD would have improved) suggests that GI GVHD contributed to systemic absorption. If, as our case report suggests, oral vancomycin, which is generally considered to be nonabsorbable, can be absorbed in instances of severe GVHD, with or without severe CDAD, as a result of impaired intestinal integrity, might other non-absorbable drugs also be absorbed? Two agents that are commonly used in this patient population include rifaximin and budesonide. A combination of oral vancomycin and rifaximin has also been used to treat recurrent or persistent CDAD (13). Absorption of rifaximin could potentially lead to metabolic drug interaction with drugs such as azole antifungals or calcineurin inhibitors; and increased levels of systemic steroids could increase the risk of infection. While this warrants further investigation, it is essential to be aware of the potential for absorption of these 'non-absorbable' drugs in patients with GI GVHD.

The third question raised is the seemingly dose-dependent absorption that is noted in all cases where significant absorption has been seen (3–5). A dose of 125 mg every 6 h has been found to be equivalent to 500 mg every 6 h for the treatment of CDAD (9). This would imply no added benefit in utilizing the higher dose. The decision to use a 500 mg dose over a 125 mg dose in this patient population could increase the risk of accumulation and potential toxicity.

The very conditions for which oral vancomycin is indicated—that is, severe disease marked by severe inflammation, potential renal insufficiency, and high stool outputs—may, in fact, be the very situations where oral absorption might be an issue. In treating patients with GI GVHD, clinicians need to be aware of the potential for oral absorption and, in select cases, monitoring of levels may be appropriate.

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