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Serum Levels of Crushed Posaconazole Delayed-Release Tablets

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Posaconazole (POS) delayed-release tablets (DRT) are favored over the suspension formulation due to once-daily dosing and improved absorption (1–4). However, patients with feeding tubes who are unable to swallow whole tablets are occasionally encountered in clinical practice. Generally, extended/delayed-release products should not be crushed, as crushing these medications impacts the release mechanism, resulting in loss of gradual/targeted gastrointestinal absorption (5). The lack of predictable and gradual absorption may put patients at risk of toxicity from rapid absorption or reduced total bioavailability (5).

Posaconazole DRT are unique compared to many delayed-release products. These tablets contain 100 mg of POS in a pH-sensitive solid dispersion polymer matrix milled powder (6, 7). The polymer matrix powder dissolves at small intestinal pH, thereby releasing POS for absorption, and is the same material originally studied as capsules (6, 7). POS DRT are made from this resulting powder, small amounts of excipients to facilitate tablet formation, and a cosmetic coating material (S. Dutta, Merck & Co., Inc., personal communication). Thus, crushing POS DRT theoretically should not significantly alter absorption pharmacokinetics, although there are no previously published reports of clinical experience with crushed POS DRT.

We identified 4 patients who received crushed POS DRT at a dose of 300 mg/day. This case series was approved as required by institutional review board (IRB) standards at each institution, and medical records were manually reviewed. No patient had significant POS drug-drug interactions, and crushed tablets were well tolerated. All patients had detectable serum POS levels (Table 1). Two of four patients had subtherapeutic serum levels (<0.7 μg/ml). Although less frequent, subtherapeutic serum POS concentrations are encountered in patients with normally functioning gastrointestinal (GI) tracts. Yi et al. studied POS therapeutic drug monitoring (TDM) in 100 patients administered various POS formulations. Of the 100 patients, 29 and 33 received intravenous (i.v.) and DRT, respectively. Subtherapeutic levels (≤ 0.7 μg/ml) were seen in 3.4% and 18.2% receiving i.v. and DRT, respectively, compared with 63% receiving suspension (8). Tverdek et al. also reported subtherapeutic levels (<0.7 μg/ml) in 18% (14/76) of patients receiving POS DRT for invasive fungal infection (IFI) prophylaxis (9). Posaconazole suspension via nasogastric (NG) tube is associated with reduced absorption, and it is unknown if crushed POS DRT are similarly affected (1). Importantly, trough levels of >0.7 μg/ml may also be required for IFI treatment (10).

Crushed POS DRT appear to be a viable administration route in select patients when neither i.v. nor whole-tablet administration is feasible. As half of the patients in this small series had low POS serum levels, TDM is advisable to ensure POS absorption. Dosage individualization may be useful, and adjustments should be made based on TDM with repeat serum levels. Additionally, drug-drug interactions should be reviewed to rule out non-absorption-related causes. Limitations of this study include the small sample size, retrospective nature, nonstandardized crushed POS DRT administration

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TABLE 1 Overview of patients receiving enteral posaconazole and therapeutic drug monitoring[a]

Patient	Underlying disease state(s)	Indication for POS	Crushed POS DRT route	Trough level (μg/ml)	Day of POS therapy level drawn[b]	Prior POS exposure and serum level	Comments
1	MDS post stem cell transplant	Suspected breakthrough fungal pneumonia on VOR	Oral	3.6	10	None	Tablets chewed and swallowed orally as patient refused to swallow whole tablets and no alternative enteral access. POS i.v. unavailable for outpatient therapy.
2	Double lung transplant	Invasive mucormycosis	PEJ tube	0.5	8	None	Patient previously receiving i.v. isavuconazole. Crushed POS DRT used to minimize i.v. medications at transition to rehab facility. Due to subtherapeutic level on crushed POS DRT and multifactorial QTc elevation preventing dose increase (did not recur with rechallenge at a later date; no level collected with rechallenge), patient restarted on i.v. isavuconazole.
3	MM, ALL	Suspected fungal sinusitis	PEG tube	1.5	12	300 mg POS DRT daily; no level obtained	Patient with significant dysphagia following stroke requiring PEG tube medication administration. POS i.v. unavailable for outpatient therapy.
4	Liver transplant	Breakthrough invasive fusariosis on VOR	NG tube	0.3	7	0.3 μg/ml on day 7 of i.v. POS	i.v. POS changed to crushed POS DRT to minimize i.v. medications at transition to rehab facility. Crushed POS DRT dose increased to 400 mg daily based on subtherapeutic level, but no repeat trough obtained.

[a]ALL, acute lymphoblastic leukemia; DRT, delayed-release tablet; MDS, myelodysplastic syndrome; MM, multiple myeloma; NG, nasogastric; PEG, percutaneous endoscopic gastrostomy; POS, posaconazole; PEJ, percutaneous endoscopic jejunostomy; QTc, corrected Q-T interval; SOT, solid organ transplant; VOR, voriconazole.
[b]Day of crushed DRT therapy that posaconazole trough concentration obtained.

technique, limited patient follow-up, and inability to extrapolate findings to other populations (e.g., pediatrics, severe mucositis). Further studies are warranted to more adequately assess the absorption of crushed POS DRT, the impact of dose changes, the effect of subclinical gastroparesis, and feeding tube type/location significance before routine adoption of this approach.

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