

Orogastric Administration of Crushed Darunavir Tablets for a Critically Ill Patient

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INTRODUCTION

When HIV-positive patients are critically ill and unable to take medications orally, administration of highly active antiretroviral therapy (HAART) becomes challenging. The foremost issue is the lack of parenteral formulations and oral suspensions.¹ Only limited clinical evidence directly addresses the conversion of antiretroviral drugs from the oral to the enteral route.²⁻⁷ Interruption of HAART is not an acceptable alternative, as this results in HIV viral rebound, immunodeficiency, opportunistic infections, and development of resistance to antiretroviral treatment.⁸⁻¹⁰ Altering the route of administration may affect the plasma concentration of antiretrovirals, which also affects clinical outcomes.² For example, as described in one case report, a 28-year-old HIV-positive man with diffuse large B cell-type lymphoma of the duodenum was taking the liquid or powder formulations of lopinavir-ritonavir, abacavir, and lamivudine (at standard adult doses) by oral ingestion, with suppression of the viral load to less than 400 copies/mL.² Development of a duodenal obstruction necessitated insertion of a percutaneous jejunal feeding tube (located ≥ 35 cm distal to the ligament of Treitz). HAART was reinitiated via the jejunostomy, leading to HIV viral rebound (to 11 000 copies/mL), undetectable serum concentration of lopinavir, and development of resistance to lamivudine (M184V mutation). Gastric bypass surgery was performed to connect the gastric corpus to the jejunum (20 cm distal from the ligament of Treitz). HAART, including lopinavir-ritonavir (oral liquid), abacavir, and tenofovir, was restarted, and measurement of serum lopinavir concentration 18 weeks later demonstrated adequate absorption of the medication, with HIV viral suppression (to 52 copies/mL).

Darunavir is an HIV-1 protease inhibitor recommended for combination HAART regimens for both treatment-naïve and treatment-experienced patients.^{1,11} This antiretroviral agent must be administered with ritonavir and food to enhance its pharmacokinetic profile and to ensure adequate antiretroviral activity.¹² The absolute bioavailability of darunavir without

ritonavir is only 37%¹²; however, when darunavir is administered concurrently with ritonavir, systemic exposure to darunavir increases 14-fold.¹² Limited data suggest adequate absorption of crushed darunavir tablets, both when swallowed and when administered via various enteral tubes.^{13,14} This report describes a case in which crushed darunavir tablets were administered to a critically ill patient through an orogastric feeding tube.

CASE REPORT

A 44-year-old man was transferred from an outside hospital to Virginia Commonwealth University Medical Center.* The patient had newly diagnosed (27 days previously) HIV infection and AIDS (baseline HIV viral load 269 820 copies/mL; CD4 lymphocytes 9/mm³), *Pneumocystis jirovecii* pneumonia, cytomegalovirus viremia, and transverse myelitis. The patient was admitted to a general internal medicine service for management of the transverse myelitis. Within a day, the patient was transferred to the medical respiratory intensive care unit (ICU) for management of respiratory distress. Fourteen days before transfer to the authors' facility, HAART (by oral administration) had been initiated. This therapy consisted of a fixed-dose combination tablet emtricitabine 200 mg – tenofovir 300 mg once daily and darunavir ethanolate 600-mg tablet with ritonavir 100-mg capsule twice daily (no genotype on record). This antiretroviral regimen was continued at the authors' facility, and the patient was tolerating oral administration of the medication. Additional concurrent oral medications included azithromycin 250 mg 5 times weekly, esomeprazole 40 mg daily, and sulfamethoxazole 1600 mg – trimethoprim 320 mg every 8 h. IV medications included foscarnet 6000 mg (body weight 72 kg), ganciclovir 350 mg every 12 h, and methylprednisolone 250 mg every 6 h. The patient's renal function and hepatic synthetic function were normal on admission.

*Patient consent was not obtained for publication of this report, because the patient died before the report was written.

On ICU day 11, the patient's respiratory status declined further, and endotracheal intubation was required. An orogastric tube (14 French, 48-in [122 cm] Salem Sump dual-lumen stomach tube, Covidien, LLC) was inserted, and medication orders were modified to facilitate orogastric administration. Specifically, ritonavir oral solution was substituted for capsules, and the fixed-dose combination emtricitabine–tenofovir tablet was crushed to a fine powder using a commercially available tablet-crushing system (Silent Knight tablet crushing system, Links Medical Products Inc.). Because the tablet formulation of darunavir ethanolate (Prezista, Janssen Therapeutics) was soluble in water and was not an extended- or delayed-release formulation, tablets of this drug were crushed using the same apparatus.¹² Once crushed, the darunavir powder was placed into a medicine cup and diluted with 15–20 mL of warm tap water. Before administration of the medication, continuous enteral feeding was paused and the orogastric tube was flushed with water. The diluted medication was administered with a 60-mL latex-free polypropylene catheter tip syringe for irrigation, followed by another water flush and resumption of enteral nutrition. This procedure is consistent with published methods for administering medications via an enteral feeding tube.¹⁵ The patient remained on continuous enteral nutrition throughout the ICU stay, without any episodes of high gastric residual volume (≥ 300 mL) or emesis, and no signs or symptoms of intestinal ischemia or perforation. The patient remained hemodynamically stable throughout the ICU course, with low-dose IV norepinephrine being used for only 13 of 342 enteral nutrition hours.

Only limited evidence supports orogastric administration of darunavir tablets, so trough concentration of plasma darunavir was measured (via high-performance liquid chromatography at National Jewish Health, Denver, Colorado) after 12 days of orogastric administration of the drug, to ensure adequate absorption.¹ The patient was receiving darunavir doses at 1000 and 1800, according to the hospital's standardized intervals for twice-daily medication administration, and the sample for measurement of darunavir trough concentration was drawn at 0930, i.e., 15.5 h after the previous dose and 0.5 h before the next scheduled dose. The measured trough concentration was 6160 ng/mL (recommended median reference value 3300 ng/mL [range 1260–7370 ng/mL]).¹ Additionally, quantitative HIV-1 RNA was measured on ICU day 5 (pre-intubation) and day 18 (post-intubation day 7). No clinically significant change in the HIV viral load occurred after the route of darunavir administration was altered (79 copies/mL and 125 copies/mL, respectively). CD4 lymphocyte counts on ICU day 5 and day 18 were 28 and 3/mm³, respectively. On ICU day 26, acute kidney injury developed. The patient's synthetic hepatic function (coagulation status)

remained normal; however, alanine transaminase increased (2.0- to 8.5-fold) throughout the hospital course. Unfortunately, the patient's clinical condition continued to deteriorate, comfort measures were pursued, and the patient died after 27 days of intensive care.

DISCUSSION

In general, oral solutions and suspensions are preferred for orogastric or nasogastric administration of drugs.¹⁵ However, darunavir oral suspension 100 mg/mL was not commercially available at the time of this patient's ICU stay.¹² This new formulation is suitable for adult patients with dysphagia.¹² In a phase I, open-label, randomized crossover study, 17 healthy adult volunteers received a single 600-mg dose of darunavir by oral administration in either the tablet (two-300 mg tablets) or suspension (6 mL of 100 mg/mL) formulation with ritonavir 100 mg in the fed state. Pharmacokinetic bioequivalence between the formulations has been demonstrated.¹⁶ Additionally, when darunavir suspension with ritonavir (standard doses) was administered to 18 patients for 6 days, the pharmacokinetic profile was similar to that obtained for historical HIV-positive controls receiving darunavir tablets.¹⁶ Further pharmacokinetic studies evaluating darunavir suspension in adult HIV-infected patients are warranted.

Although adequate plasma concentration appears to have been achieved through enteral administration of crushed darunavir tablets, there were some limitations to patient care in the case reported here. In particular, darunavir trough concentration was measured only once. Nonetheless, the results obtained suggest that altering the available darunavir formulation (by crushing the tablets) resulted in a therapeutic trough concentration, with virologic suppression, in a mechanically ventilated HIV-infected patient receiving continuous enteral nutrition. The patient was newly diagnosed with AIDS, was HAART-naïve, and was being treated for several opportunistic infections, all of which complicate any conclusions drawn. Immune reconstitution inflammatory syndrome (IRIS) was a concern for this patient, as the CD4 lymphocyte count initially increased to 28/mm³ on ICU day 5. Although it is well known that prednisolone concentrations are increased with protease inhibitors, high-dose corticosteroids were continued during the hospital stay to concurrently treat a possible IRIS event and the patient's transverse myelitis.¹⁷ Additionally, HAART may lead to several adverse effects, including hypertriglyceridemia, elevated pancreatic or hepatic enzymes, diarrhea, and rash. Baseline cholesterol, amylase, and lipase were not measured, but the alanine transaminase increased throughout the hospital course. Although hepatic failure leads to decreased antiretroviral elimination, the patient's hepatic synthetic function (as measured by coagulation parameters and total bilirubin) never increased, and thus darunavir metabolism should not have been

Table 1. Data on Alternative Administration of Darunavir Tablets for HIV-Positive Patients

Study	Study Design	Dose of DRV/RTV	Route of Administration	Serum Concentration of Darunavir (ng/mL)
Scholten et al. ¹³	Case report (57-year-old man)	600/100 mg bid	Crushed tablets by mouth	6950 (10 h post-dose)
Scholten et al. ¹³	Case report (48-year-old woman)	600/100 mg bid	Stomach tube	4430 (5 h post-dose) 5210 (3 h post-dose at 6 months after initial measurement)
Taegtmeyer et al. ¹⁴	Case report (43-year-old man)	600/100 mg bid	Nasogastroduodenal tube via gastric port	6100 at 2 h post-dose 5700 at 6 h post-dose
Current report	Case report (44-year-old man)	600/100 mg bid	Orogastric tube	6160 (15.5 h post-dose; sample drawn just before next dose)

DRV/RTV = darunavir/ritonavir.

affected.¹⁸ The patient appeared to tolerate HAART without gastrointestinal intolerance, as liquid bowel movements occurred on only 4 ICU days. No rash occurred during the hospital stay, but dermatologic complications may have been suppressed by concurrent administration of corticosteroids. Future pharmacokinetic and pharmacodynamic studies would ideally measure darunavir trough concentration multiple times in HIV-infected patients ingesting crushed darunavir tablets.

Three previous case reports^{13,14} support the administration of crushed darunavir tablets (Table 1). Two of these reports involved administration of crushed darunavir tablets via various feeding tubes (nasogastroduodenal tube via gastric port and stomach tube), whereas the third involved the patient swallowing the crushed tablet. It is not known whether antiretroviral absorption would be similar in other anatomically altered HIV-positive patients (those with nasojejunal tube, short bowel syndrome, or gastric bypass). Moreover, a single case report documented a decrease in lopinavir concentrations and HIV viral rebound with administration through a percutaneous jejunal feeding tube.²

Although the oral suspension of darunavir is now commercially available in some countries, including the United States, some hospital formularies may not opt to carry both the tablet and the liquid formulations. In addition, the oral suspension is not yet available in Canada. The present report and 3 previously published reports support the administration of crushed darunavir tablets both orally and via enteral tubes. Given that HIV-positive patients are living longer and experiencing age-related medical complications,¹⁹ additional data evaluating the pharmacokinetic and pharmacodynamic parameters of antiretrovirals are necessary to optimize dosing and clinical outcomes in patients who are unable to swallow intact tablets and capsules.

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ON THE FRONT COVER

Sunfire Assiniboine Park, Winnipeg, Manitoba



special moments and the beauty around her, even if it involves

This photograph captures a stunning sunrise early one morning in November 2012. The photographer, Elaine O’Keeffe, is a cousin of pharmacist and CSHP staff member Catherine Lyder. Elaine has always loved taking photos, capturing those

leaving home early to take a picture en route to work, as was the case for this photo. She aims to capture the inner character of whatever or whoever she is photographing, bringing out its vibrancy and beauty so that others may see it too. More of her work can be seen at www.elaineokeeffephoto.com. This issue’s cover photo was taken with a Canon EOS 7D camera.

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