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Acceptable Raltegravir and Etravirine Concentrations in Plasma when Administered via Gastrostomy Tube

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Abstract

Background—Circumstances arise in clinical practice when alternative antiretroviral formulations are urgently needed for those unable to take available tablet or capsule formulations orally. Currently, only a few agents can be administered with commercially available liquid, powder or parenteral formulations.

Methods—A patient infected with multidrug-resistant human immunodeficiency virus (HIV) and hepatitis B required antiretroviral therapy via a gastrostomy because of esophageal perforations. Tablets of the patient's current regimen of raltegravir, etravirine, tenofovir and emtricitabine (Truvada®) were crushed or dispersed and mixed with water and administered via the gastrostomy tube. Plasma samples 2-hour and 12-hour post dose were obtained and drug concentrations quantitated using validated assays. Results were compared to those in published pharmacokinetic studies from HIV-Infected persons and healthy volunteers.

Results—The 2 and 12-hour post dose measured raltegravir concentrations were 1,220 ng/mL and 446 ng/mL, respectively. The 2 and 12-hour post dose etravirine concentrations were 212 ng/mL and 274 ng/mL; emtricitabine was 1148 and 164 ng/mL and tenofovir was 320 and 94 ng/mL respectively.

Conclusions—Plasma concentrations of raltegravir, etravirine, emtricitabine and tenofovir when administered via gastrostomy tube compared favorably with published values.

Keywords

Raltegravir; Etravirine; Plasma concentrations; Pharmacokinetics; gastrostomy tube

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Conflict of Interest Statements

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Introduction

Circumstances occasionally arise in clinical practice when oral administration of antiretroviral therapy is not feasible, but provision of treatment is urgently required¹. Currently, no Department of Health and Human Services (DHHS) preferred regimen for antiretroviral-naïve persons could be administered with commercially available liquid, powder or parenteral formulations². Liquid or powder formulations are available for all individual nucleoside reverse transcriptase inhibitors except tenofovir, which can be crushed³. From the non-nucleoside reverse transcriptase inhibitor class, there is a liquid formulation of nevirapine, efavirenz can be dispersed in water⁴ and although there are no data on crushing efavirenz tablets, capsules may be emptied and mixed with a small amount of food or liquid^{5,6}. There is an expanded access program of efavirenz liquid formulation for children and adolescents⁷. Protease inhibitors have liquid or powder formulations available except atazanavir, darunavir and indinavir. Lopinavir/ritonavir concentrations may be significantly reduced when given as the crushed tablet⁸. There are no liquid formulations or data on crushing maraviroc or raltegravir. We present a case of esophageal perforation in a patient requiring salvage therapy for multidrug resistant HIV, although unable to take anything by mouth. The regimen included raltegravir, efavirenz, emtricitabine and tenofovir, and all drugs had to be administered through a gastrostomy tube.

In the absence of data to guide appropriate dose modifications, we measured plasma concentrations of raltegravir, efavirenz, emtricitabine and tenofovir. To our knowledge, this is the first report of plasma efavirenz concentrations following gastrostomy tube administration by tablet dispersion in water in an HIV-infected person, and the first of raltegravir, emtricitabine and tenofovir concentrations when the tablets are crushed, extemporaneously compounded and administered via the same route.

Case report

A 52 year-old African American male with advanced multidrug resistant HIV infection and chronic hepatitis B coinfection who had failed several antiretroviral regimens and developed multiple HIV resistance-associated mutations, was started on a salvage antiretroviral regimen of raltegravir, efavirenz, emtricitabine and tenofovir. Genotypic and phenotypic resistance testing indicated susceptibility to efavirenz and raltegravir, partial susceptibility to tenofovir, and resistance to emtricitabine. Tenofovir and emtricitabine were prescribed largely to treat the hepatitis B co-infection. After receipt of this regimen for 2 months, the HIV viral load was <50 copies/mL, and CD4 count 199 cells/mm³; the hepatitis B viral load was also below the limit of detection (< 50 IU/mL). Concomitant medications included sulfamethoxazole-trimethoprim, entecavir, posaconazole, omeprazole, zolpidem, oxycodone/acetaminophen, and enteral nutrition with soluble fiber and 29% fat.

In June of 2009, the patient developed ulcerative esophagitis with perforation, requiring the insertion of a percutaneous endoscopic gastrostomy (PEG) tube and a no food by mouth restriction to allow adequate time to heal the ulcers. All medications and nutrition were administered via the gastrostomy tube during this time. With very limited alternative antiretroviral agents with potential utility in this case, no other dosage forms available, and the need to continue antiretroviral therapy, the decision was made to crush the raltegravir, emtricitabine and tenofovir and administer them via the gastrostomy tube; efavirenz was administered by dispersion of the tablet in water and then administration via the gastrostomy tube. During the hospitalization and subsequently at a skilled nursing facility, the staff was instructed to crush raltegravir, mix it with 60 mL of warm water, allow it to dissolve and then draw up the solution with a syringe and administer via the gastrostomy tube. The procedure for crushing and administration of emtricitabine and tenofovir (as the crushed Truvada® tablet) was the same. As the stability of the compounded preparations is unknown,

preparations were made immediately before administration. Medications dosed once daily were administered in the morning. Representatives from the manufacturer⁹, internet sources of drug information¹⁰ and the Isentress[®] Summary of Product Characteristics from the European Medicines Agency¹¹ all recommended that raltegravir tablets should not be crushed. Therefore, we decided that therapeutic drug monitoring should be initiated to ensure therapeutic concentrations of raltegravir and continued viral suppression.

Plasma samples were drawn during scheduled clinic appointments for real-time quantitation of raltegravir plasma concentrations after consistent administration for 2 months. Samples were obtained 2-hour post raltegravir dosing on one occasion, and 12-hour post dosing at a visit approximately one month later. Sampling times were chosen to approximate peak and trough levels. The last tube feeding was 7 hours prior to the 2 hour sample, and 3 hours prior to the 12 hour sample. Etravirine, emtricitabine and tenofovir concentrations were determined subsequently. Raltegravir concentrations in plasma were quantitated using a validated tandem mass spectrometry assay. The assay range was 10 to 10,000 ng/mL with interday variability of 0.8 to 8.8% across quality controls and a mean relative error of less than 7%. Etravirine concentrations were quantified by ultra high pressure liquid chromatography. The range of this assay was 20 to 20,000 ng/ml with precision and accuracy less than 6%. Emtricitabine and tenofovir concentrations were quantified by high pressure liquid chromatography-mass spectroscopy. The range of the assay was 10 to 1,500 ng/ml, and precision and accuracy were less than 8%, except at the limit of quantitation where it was less than 11%. Table 1 presents the measured raltegravir, etravirine, emtricitabine and tenofovir plasma concentrations in this patient, and comparative data from pharmacokinetic studies in HIV-infected persons and healthy volunteers.

The measured raltegravir concentrations indicated the crushed tablet was absorbed when administered via the gastrostomy tube with concentrations comparable to those in HIV-infected persons and healthy volunteers. Therefore, raltegravir (as well as etravirine, emtricitabine and tenofovir) administration was continued.

No drug toxicities were observed with administration of this regimen. The HIV and hepatitis B viral loads remained undetectable and the CD4 count increased to 238 cells/mm³; however, the fistulizing esophagitis failed to heal despite aggressive medical treatment including insertion of large stents. This was thought to be in part due to the patient's noncompliance with prohibition of eating solid food, which caused occlusion of the stent and ongoing inflammation of the surrounding tissues. He continued to lose weight and experience constant pain, and after 15 months of treatment, decided to transition to palliative care and died at home.

Discussion

Overall, the plasma concentrations of prescribed antiretroviral agents delivered via a gastrostomy tube in this patient compared favorably with published values. The 2-hour post dose measured raltegravir concentration, which occurs near the usual time to maximal concentrations of three hours, was 1,220 ng/mL and falls within the range of maximum concentrations observed in HIV-infected persons. The 12-hour raltegravir concentration of 446 ng/mL is within the bounds of reported trough concentrations in healthy volunteers at steady state concentrations, including consideration for food^{18,19}. The 12-hour post dose etravirine concentration of 274 ng/mL in this patient agrees very well with values in HIV-infected persons.

The pharmacokinetic characteristics of raltegravir are characterized by high interpatient variability, and food has different effects on absorption and disposition. When compared

with administration to healthy volunteers in the fasted state, the geometric mean ratio for the maximum raltegravir concentrations was 0.48 following a low fat meal, 1.05 following a moderate fat meal, and 1.96 after a high fat meal. Food also had a variable effect on 12-hour post dose (trough) concentrations: the geometric mean ratios were 0.86, 1.66 and 4.13 following low, moderate and high fat meals, respectively, compared with fasted¹⁸. In this patient, both nutrition and drug administration were accomplished via the gastrostomy tube, and food and fat may have affected the absorption and disposition of raltegravir. A higher trough concentration might also arise because of a difference in the rate or extent of raltegravir absorption when delivered via gastrostomy tube or due to a drug-drug interaction with omeprazole as co-administration increases raltegravir plasma levels in healthy volunteers²⁰. As illustrative of concentrations in HIV-infected persons, the median AUC was 8160 ng*h/mL with a range of 1685 to 12770 ng*h/mL at steady-state with a dose of 400 mg twice daily administered in the fasted state¹². The median C_{max} was 2880 ng/mL with a range of 355 to 4520 ng/mL and the median 12 hour post dose concentration was 72 ng/mL with a range of 29 to 118 ng/mL. The major clearance route for raltegravir is hepatic metabolism, primarily via UDP-glucuronosyltransferase (UGT1A1). Etravirine reduces raltegravir concentrations presumably through induction of UGT1A1; trough raltegravir concentrations were reduced 34% with coadministration of etravirine in one study with healthy volunteers²¹. Conversely, tenofovir has been shown to increase raltegravir concentrations in HIV-infected persons. The raltegravir area under the curve and maximum concentrations were increased 49% and 64%, respectively, when given with tenofovir compared²². Trough concentrations of raltegravir in our patient were towards the high end of the expected range.

Etravirine concentrations in plasma, like raltegravir, exhibit a high degree of interpatient variability. Food significantly increases absorption and current dosing guidelines recommend administration with food. The median time to peak etravirine concentration is 4 hours. The measured 2-hour post dose concentration in this patient possibly occurred prior to the time of maximum concentrations of 4 hours, and thus could be expected to be lower than the usual maximum concentration. A pharmacokinetic study of etravirine in 25 HIV-infected persons taking 200 mg twice daily (taken with food) found median peak concentrations of 525 ng/mL with a range of 285 to 4,980 ng/mL. The median value of the 12-hour post dose concentration was 240 ng/mL with a range of 142 to 4,850 ng/mL¹⁴. All subjects in this pharmacokinetic study were also receiving darunavir/ritonavir, which reduces etravirine concentrations by 37%¹⁵. Our decision to administer etravirine dispersed in water was based on data from a healthy volunteer study in which the area under the curve and maximum concentration of etravirine after administration of a single dose 100 mg tablet dispersed in 100 mL of water were shown to be bioequivalent with the 100 mg tablet swallowed⁴. Co-administration of drugs that are substrates for CYP3A4 may also affect etravirine plasma concentrations, such as the posaconazole co-administered to the patient in this report. Although this combination has not been studied, according to the manufacturer's produce information, posaconazole may increase plasma concentrations of etravirine²³.

Emtricitabine and tenofovir are well absorbed orally and may be administered without regard for food, although the oral bioavailability of tenofovir is increased following a high-fat meal³. Maximum concentrations of both usually occur approximately two hours post dose, and elimination half-lives range from 10 – 17 hours²⁴. There are no published data on the impact on plasma concentrations of crushing tablets for administration via gastrostomy tube. Importantly, the 2-hour post dose concentrations of emtricitabine and tenofovir measured following crushed tablet administration in this patient compare very well with maximum concentrations in HIV-infected persons and healthy volunteers (Table 1). The concentrations measured at 12 hours post dose are not true trough values, and would decrease, perhaps up to 50%, by the time of the next scheduled dose 12 hours later (once

daily dosing). The actual troughs would be consistent with expected values based on data in HIV-infected persons and healthy volunteers and usual outpatient pharmacokinetic variability^{16,25}. Relationships between plasma concentrations of NRTIs, their intracellular pharmacologically active moieties, and virologic response have not yet been established. Therefore, monitoring of plasma or intracellular NRTI concentrations in an individual patient as a guide for therapeutic response is not recommended in routine clinical practice². However, measurement of plasma concentrations is acknowledged to provide information on alterations in NRTI absorption and disposition, such as in studies of drug-drug interactions.

There are limitations to the strength of these observations. Only two plasma concentrations were obtained in this subject, and the 2- and 12-hour post dose concentrations were not collected following the same dose. The ideal sampling schedule would be the collection of serial concentrations following observed administration of the doses over the 12 hour dosing interval for raltegravir and etravirine and 24-hour dosing interval for emtricitabine and tenofovir. Because both nutrition and drug administration was accomplished via the gastrostomy tube, we cannot be confident as to the exact condition of whether absorption occurred in the presence or absence of food. A higher trough concentration might also arise because of a difference in the rate or extent of raltegravir absorption when delivered via gastrostomy tube. Etravirine concentrations in this patient likewise appeared consistent with expectations. A concentration measured 2 hours following a dose of etravirine would typically reflect the process of absorption and occur prior to the time of maximum concentrations of 4 hours, and thus could be expected to be lower than the usual maximum concentration. Nonetheless, all drug concentrations were measurable and fall within expected ranges following standard oral dosing.

Collectively, these pharmacokinetic data suggest raltegravir, etravirine, emtricitabine and tenofovir absorption was not compromised when they were administered via a gastrostomy tube. These findings provide a basis for further investigation of the pharmacokinetic, safety and tolerance, and antiretroviral response to raltegravir, etravirine, emtricitabine and tenofovir administration when the oral route of administration is compromised. Furthermore, this case illustrates one of many scenarios in which pharmacokinetic data on alternative administration of antiretrovirals and alternative formulations, when the oral route of administration is not possible, are urgently needed.

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Table 1

Raltegravir, Etravirine, Emtricitabine and Tenofovir Concentrations in Plasma

Drug	Subjects	Plasma Concentrations (ng/mL) by Time Post Dose (hr) and (ranges, $\pm$ SD, or CV%)		
		2	C _{max} ^a	12
Raltegravir	This patient	1220		446
	HIV-infected patients ^{d,12}		2882 (355-4520)	72 (29-118)
	Healthy volunteers ^{c,13}		634 (252-9429)	60 (15-566)
Etravirine	This patient	212		274
	HIV-infected patients ^{b,14,15}		525 (285-4980)	240 (142-4850)
	Healthy volunteers ^{c,15}		959 ($\pm$ 278)	530 ($\pm$ 173)
Emtricitabine	This patient	1148		164
	HIV-infected patients ^{e,16}		1514 (771-2316)	167 (45-884) ^f
	Healthy volunteers ^{g,16}		1600 (26%)	80 (26%) ^f
Tenofovir	This patient	320		94
	HIV-infected patients ^{e,17}		367 (178-643)	77 ^f (30.6-140)
	Healthy volunteers ^{g,16}		252 (25%)	52 (25%) ^f

^a C_{max} occurred at a median of 3 hours post dose for raltegravir, 4 hours for etravirine, 1.5 hours for emtricitabine and 0.75 hours for tenofovir.

^b Median values; raltegravir administered in a fasting state

^c Geometric mean values; raltegravir and etravirine administered following a moderate fat meal

^d Median values; etravirine was administered following a meal and given concurrently with darunavir/ritonavir in all subjects

^e Median values

^f Measured concentration at 24 hours post dose

^g Mean values