Pharmacokinetics of Enfuvirtide in a Patient with Impaired Renal Function

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Enfuvirtide is the first member of the fourth class of antiretroviral drugs to become available. We present a case report of a human immunodeficiency virus (HIV)-positive patient with mild renal impairment who developed severe renal impairment secondary to tenofovir therapy while receiving enfuvritide. Because the patient’s pharmacokinetic profile was not significantly altered, compared with that of HIV-infected patients with normal renal function, no dose modifications were required.

Enfuvirtide is the first member of the fourth class of antiretroviral drugs (i.e., the fusion inhibitors) to be developed [1]. Data on the efficacy and safety of enfuvirtide from the T-20 versus Optimized Regimen Only (TORO) 1 and TORO 2 phase III clinical trials have been reported elsewhere [2, 3]. The pharmacokinetic profile of enfuvirtide was established in a clinical trial involving 12 HIV-infected individuals. It was shown that enfuvirtide has a mean steady-state volume of distribution (± SD) of 5.5 ± 1.2 L following the administration of a single 90-mg intravenous dose [4], and it has a mean terminal elimination half-life (± SD) of 3.8 ± 0.6 h and an apparent clearance of 1.7 ± 0.4 L/h following a single 90-mg subcutaneous injection [4]. Subcutaneous administration of enfuvirtide results in a slow and protracted absorption phase and a relatively flat steady-state plasma concentration-time profile, supporting twice-daily dosing.

Because enfuvirtide is a peptide, it is expected to undergo catabolism to its constituent amino acids and is not expected to be cleared by the renal excretion route. To date, there have been no formal studies and no published data on enfuvirtide pharmacokinetics in patients with renal impairment. However, analysis of plasma concentration data from patients in clinical trials indicates that the clearance of enfuvirtide is not affected in patients with creatinine clearance ≥35 mL/min [5]. The effect of creatinine clearance <35 mL/min on enfuvirtide clearance has not been determined. We report a case involving an HIV-positive patient with renal impairment who received enfuvirtide.

Case report. A 26-year-old white, antiretroviral therapy–experienced, HIV-positive man with mild renal impairment (baseline [study day −1] creatinine clearance, 48.5 mL/min; baseline serum creatinine level, 145 µmol/L; figure 1) was enrolled into a phase III trial (TORO 2 [3]) and randomized to receive enfuvirtide plus an optimized background (OB) antiretroviral regimen. The patient had a baseline plasma HIV RNA load of 5.6 log10 copies/mL and a CD4+ cell count of 14 cells/mm3. Approximately 10 months before enrollment, the patient had experienced renal tubular acidosis within 2 months after starting therapy with adefovir (60 mg q.d.). Renal function improved following withdrawal of adefovir. The patient had no other previous renal dysfunction.

At baseline, the patient started an OB regimen comprising didanosine (250 mg q.d.), lamivudine (150 mg b.i.d.), lopinavir/ritonavir (400/100 mg b.i.d.), and tenofovir (300 mg q.d.), and on study day 1, he commenced therapy with enfuvirtide (90 mg b.i.d.). The patient was also receiving trimethoprim-sulfamethoxazole, azithromycin, and potassium bicarbonate/potassium chloride for prophylaxis of low potassium levels secondary to impaired renal function, which were ongoing at screen 1. On day 13, severe renal impairment was noted (serum creatinine level, 338 µmol/L; creatinine clearance, 15.7 mL/min); on day 14, a local laboratory (Western General Hospital, Edinburgh) determined the patient’s serum creatinine level to be 425 µmol/L. Enfuvirtide therapy was interrupted, tenofovir therapy was discontinued, and other antiretroviral dosages were adjusted, leaving the patient with a regimen of didanosine (100 mg q.d.), lamivudine (100 mg q.d.) and lopinavir/ritonavir (400/100 mg b.i.d.). Renal biopsy findings revealed renal tubular toxicity, judged to be attributable to tenofovir therapy. The patient also reported truncal rash, nausea, depression (for which mirtazapine was prescribed), and vomiting (for which metoclopramide was prescribed).

By day 29, the patient’s renal function had improved and stabilized (6 nonfasting serum samples, obtained between day 21 and day 30, had creatinine levels of 244–277 µmol/L; mean creatinine level, 256.5 µmol/L; day 27 creatinine clearance, 26.4 mL/min). The patient’s HIV RNA load was 4.7 log10 copies/mL, and the patient’s CD4+ count had increased to 44 cells/...
Figure 1. Serum creatinine levels during the course of the study. The inset figure shows the plasma enfuvirtide (ENF) concentration-time profile for a patient with moderate renal impairment after a single 90-mg subcutaneous injection of ENF, compared with historical data (mean ± SD) obtained from patients without renal impairment. Diamonds, data for the patient with moderate renal impairment; solid line, historical data from patients with normal renal function (n = 12) [4]; black circles, protocol-specified measures; white circles, local laboratory values. BL, baseline; PK, pharmacokinetic; S1, screen 1 (study day −71); S2, screen 2 (study day −34).

mm². Because enfuvirtide is unlikely to be cleared by renal excretion and because tenofovir was considered to be the attributable agent for this event, it was deemed relatively safe to rechallenge with enfuvirtide. Fourteen days after interruption of enfuvirtide therapy, the patient received rechallenge with a single 90-mg subcutaneous dose, and 5 additional blood samples were obtained at time-points up to a nominal 12 h after the dose was administered. These blood samples were stored until analysis for plasma enfuvirtide using a validated liquid chromatography-tandem mass spectrometry method [6].

The plasma enfuvirtide concentrations, calculated as the mean value for each sample, were 0, 0.48, 2.73, 5.20, and 3.62 μg/mL at times 0 (predose), 1.25, 3.42, 6.92, and 11.42 h after dosing, respectively (actual sampling times) (figure 1). All data points were within 1 SD of the mean for historical data from HIV-infected individuals with normal renal function who received a single 90-mg subcutaneous dose of enfuvirtide [4].

Tenofovir therapy was permanently discontinued. The severe renal impairment was not considered to be related to enfuvirtide therapy. Enfuvirtide (90 mg b.i.d.) was recommenced as part of the patient’s regimen, comprised of didanosine (100 mg q.d.), lamivudine (100 mg b.i.d.), saquinavir (1000 mg b.i.d.), and ritonavir (100 mg b.i.d.). Thereafter, the patient continued to receive enfuvirtide with no deterioration in renal function during the following 8 months.

Discussion. This case illustrates 2 points. First, enfuvirtide was unlikely to have caused the deterioration in renal function, as predicted by an understanding of the metabolism of enfuvirtide and other confounding factors of preexisting medical history and concomitant medication and as confirmed by rechallenge, which caused no further deterioration. The findings of the renal biopsy further suggested that the renal impairment was indeed related to tenofovir, rather than to enfuvirtide. This patient had a number of predisposing factors, including a history of chronic renal impairment and a history of renal tubular acidosis secondary to adefovir. Tenofovir has been previously associated with different forms of renal impairment, including cases of Fanconi syndrome, nephrogenic diabetes insipidus, and renal failure [7–11]. Tenofovir has also been associated with damage to proximal tubular cells of the kidney [8, 11]. In addition, azithromycin therapy can cause interstitial nephritis and acute renal failure, and trimethoprim-sulfamethoxazole can cause renal disorders, including interstitial nephritis.

Second, the concentration-time profile of the patient with renal impairment was not significantly different from the historical data, which shows a similar profile, and suggests that the plasma enfuvirtide levels in this patient are similar to those in renally competent patients. Therefore, no dose adjustment of enfuvirtide was required. However, data from this patient are somewhat limited because of the lack of available data from
>12 h after dosing. Further investigation with a larger population of patients would be required for definite recommendations, but given our knowledge of the metabolism of enfuvirtide, a similar result would be expected.

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**References**


