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【 CASE REPORT 】

An HIV-infected Patient with No Serious Adverse Events after Overdosing on Raltegravir

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Abstract:
Patients with HIV infection represent a high-risk group for medication overdose because of the high frequency of complicating psychiatric disorders. Raltegravir is well-known for its low frequency of adverse effects. We herein report a 42-year-old Japanese man with HIV infection who was hospitalized 6 hours after overdosing with 24,000 mg of raltegravir in a suicide attempt. No serious adverse events occurred, although the plasma concentration of raltegravir at 18 hours after the overdose was 79,871.1 ng/mL. Raltegravir may be well-indicated for HIV patients at risk of overdosing.

Key words: raltegravir, overdosing, adverse event, pharmacokinetics, attempting suicide

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Introduction

Patients with HIV infection often show comorbid psychiatric disorder (1), and the administration of antiretroviral drugs, such as efavirenz and dolutegravir, may cause psychiatric symptoms, even in patients without initial psychiatric disorder (2, 3).

Patients with depression sometimes deliberately overdose on drugs when attempting suicide. The frequency of drug overdose has been increasing recently, representing the largest cause of accidental death among HIV patients (4). Several case reports have described patients with HIV overdosing on antiretroviral drugs, including manic syndrome-induced efavirenz overdose (5), and permanent kidney damage due to renal tubular necrosis (6) induced by tenofovir overdose.

Raltegravir is recognized as having few side effects, including a low rate of psychiatric symptoms, and showing few interactions with psychiatric drugs (3). It also offers a wide safety margin in terms of the plasma concentration, and the usefulness of high-dose once-daily oral administration has been described in some recent reports (7).

To our knowledge, only one case report appears to describe overdosing on raltegravir (16,000 mg). No serious adverse events developed in that patient (8). However, the serum concentration of raltegravir at the evaluation was 0 μg/mL, because the patient was admitted to the hospital 96 hours after overdosing on raltegravir. The adverse effects caused by an excessively high plasma concentration of this drug therefore remain unknown.

Case Report

A 42-year-old Japanese man was transferred to the hospital 6 hours after overdosing on 24,000 mg of raltegravir. He had presented to a police station, where he had reported overdosing. His medical history included a carrier status for hepatitis B virus and depression. He had been diagnosed with HIV infection nine years earlier and had been started on the administration of tenofovir/emtricitabine and efavirenz six years earlier. His prescription had been changed from efavirenz to raltegravir due to mental disorders five years earlier. He first developed intermittent bigeminy four years earlier and had developed this symptom again three days before the overdose. Regular medications other than antiretroviral drugs included eszopiclone at 3 mg/day and alprazolam at 0.8 mg/day. The patient had not overdosed on these drugs.

He presented with transient mild nausea and abdominal pain on admission. His vital signs showed no abnormalities on admission. Although he appeared slightly disoriented,

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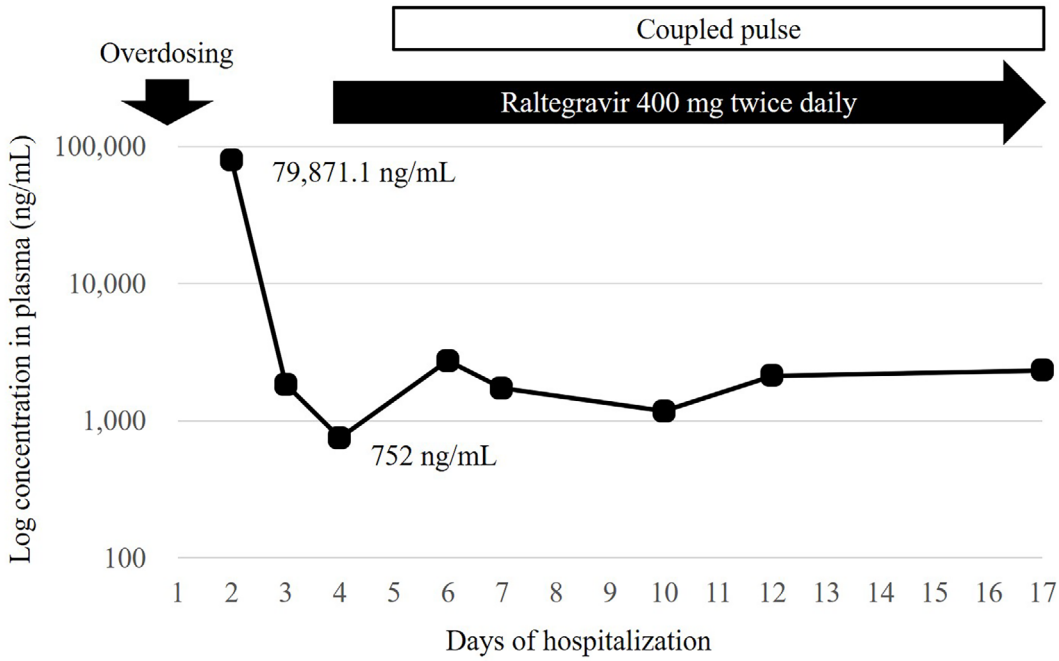

Figure. **The clinical course and plasma concentration of raltegravir.**

neither cranial nerve nor cerebellar ataxia was found. His CD4-positive T-cell count was 402 cells/μL, and the HIV1-RNA viral load was below the limit of detection. The hepatitis B virus-DNA viral load was 7.5 log/mL. No abnormalities were identified in the renal function, electrolytes, or hepatobiliary enzymes, except for a slightly elevated concentration of total bilirubin (1.29 mg/dL). The blood sugar level was 60 mg/dL. Electrocardiography on admission showed sinus rhythm.

Raltegravir was discontinued, while daily tenofovir/emtricitabine was continued after hospitalization. On hospital day 4, the administration of raltegravir was resumed at 400 mg every 12 hours. Bigeminy developed from hospital days 5 to 17 (the day of discharge). During hospitalization, he did not present with headache, diarrhea, or dizziness, all of which are relatively common adverse effects of raltegravir. No hepatobiliary system disorder or elevation of serum creatine kinase was found during hospitalization, and the serum potassium concentration ranged from 4.0 mEq/L to 4.6 mEq/L. The bigeminy had disappeared by three months after discharge. The plasma concentration of raltegravir was determined at a later date from samples taken during hospitalization (Figure). The plasma concentration of raltegravir was 79,871.1 ng/mL at 18 hours after overdosing and 752 ng/mL at 66 hours, representing a half-life of 7.2 hours for this period.

Discussion

We identified two important clinical issues. First, the half-life of raltegravir in the terminal phase (7.2 hours) largely matches the theoretical value from pharmacokinetics/pharmacodynamics, even after overdosing, although the maximum blood concentration (C_{max}) and half-life in the initial phase were not evaluated in this case. Data for a single-dose administration of raltegravir (400 mg) have shown the following: maximum concentration time (T_{max}), 1.0 hours; C_{max}, 10.63 nM (5,130 ng/mL); half-life in the initial phase, 1.07 hours; and half-life time in the terminal phase, 6.9 hours (9). The plasma concentration of raltegravir is therefore easy to predict, even after overdosing. Second, raltegravir may show a wide safety margin. Rhabdomyolysis and cerebellar ataxia have been reported as serious adverse events with raltegravir (10, 11). These adverse effects were not found even when the plasma concentration was excessively elevated, as in this case. To our knowledge, no reports have described any association between raltegravir and serious arrhythmia. Known bigeminy appeared two days before overdosing and after resuming of raltegravir, rather than at the time of excessively elevated plasma concentration in this case. The relationship between the blood concentration of raltegravir and arrhythmia remains unknown.

In conclusion, the present case developed no serious adverse events despite excessively high serum concentrations of raltegravir. Raltegravir may therefore be well-indicated for HIV patients at risk of overdosing.

Author's disclosure of potential Conflicts of Interest (COI).
Toshio Naito: Honoraria, MSD.

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