Case Report

Acute Efavirenz Intoxication in a 16-year-old HIV Negative Girl: A Case Report and Literature Review

Minoo Moghimi[1], Zahra Nekoukar[1], Navid Khosravi[2, 3*]

1. Department of Clinical Pharmacy, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.
2. Department of Emergency Medicine, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
3. Department of Emergency Medicine, Razi Hospital, Mazandaran University of Medical Sciences, Qaem Shahr, Iran.

*** Corresponding Author:**
Navid Khosravi, MD.
Address: Department of Emergency Medicine, Razi hospital, Mazandaran University of Medical Sciences, Qaem Shahr, Iran.
Phone: +98 (911) 3230392
E-mail: n.khosravi@mazums.ac.ir

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ABSTRACT

Background: There are only rare case reports that revealed the efavirenz (EFV) toxicity.

Case Report: This study presents an acute intoxication with 12 g of efavirenz in a 16-year-old healthy girl whose main problem was dose-dependent neurotoxicity. No other serious EFV-related side effects were seen. Previous serious side effects of EFV were observed in HIV-infected patients who underwent long-term combination drug therapy.

Conclusion: Accordingly, in terms of the key clinical messages, serious adverse effects of efavirenz are expected to be observed in long-term use in combination with other antiretroviral drugs.

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Introduction

Intentional drug overdose (IDO) is one of the common causes of emergency room referrals in the adolescent population. While women are more likely to proceed with suicidal attempts by IDO, drug abuse poisonings are responsible for these cases in men [1]. According to one research by Meghan Gilley et al., acetaminophen, antidepressants, and non-steroidal anti-inflammatory drugs were the most common medications used for IDO [2]. Reports from the north of Iran indicate that opioids (especially tramadol) and benzodiazepines are the leading drugs involved in IDO [3]; however, IDO does not always happen with these agents, and uncommon prescribed drugs are sometimes responsible as well. Efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor used for the treatment of acquired immunodeficiency syndrome is available in a single form and in combination with other anti-HIV drugs [4]. The recommended dose is 600 mg daily and should be used in a combination regimen with a protease inhibitor or nucleoside reverse transcriptase inhibitor. The common combination formulations are EFV/emtricitabine/tenofovir (EFV/FTC/TDF) and EFV/lamivudine/tenofovir (EFV/3TC/TDF) [5]. EFV in patients receiving combinations with antiretroviral therapy can endanger several body organs, including the nervous system (dizziness, depression, insomnia, anxiety, pain, headache, drowsiness, and nervousness), skin (mild to moderate maculopapular rash), gastrointestinal (diarrhea, nausea, vomiting, increased gamma-glutamyltransferase, and amylase), endocrine and metabolic (increased serum cholesterol, high-density lipoprotein cholesterol, and triglycerides, hyperglycemia), hematologic (neutropenia), and hepatic systems (increased aspartate aminotransferase and alanine aminotransferase) [6]. In Iran, EFV is not a widely available drug and is only supplied in certain drugstores. To the best of our knowledge, this study presents the first case of EFV overdose in a 16-year-old HIV-negative female.

Case Presentation

A 16-year-old girl was brought to the emergency department 3.5 h after an intentional ingestion of 20 EFV tablets (600 mg) for a suicidal attempt. She was alert and her chief complaints were headaches, dizziness, nausea, and bloating. On arrival, vital signs were as follows: Blood pressure=100/60 mmHg, pulse rate=98 beats/min, temperature=37.2˚C, respiratory rate=18/min, and O_2 saturation=98% . The abdomen had no tenderness. The physical examination showed no abnormal points. This HIV-negative girl had no underlying disease and no history of drug use. In the emergency room, charcoal 1 g/kg and sorbitol powder 1 g/kg were ordered orally for her, and serum NaCl 0.9% 500 mL and ampule ondansetron were administered via intravenous line infusion. Her blood was checked for blood sugar, creatinine, and blood urea. The results are presented in Table 1. Complete blood counts were also ordered and she was admitted to the clinical toxicology ward. On the first day, she was hydrated with 2500 mL NaCl 0.9% every 24 h. Famotidine tablet 40 mg daily, ampule of ondansetron 4 mg PRN, blood sugar checking every 6 h, cardiac monitoring, pulse oximetry, and venous blood gas were also ordered. Acetaminophen tablet 500 mg was prescribed according to her headache.

Psychiatric consultation was requested based on the potential acute psychiatric side effects of EFV and also her suicidal ideation. Nausea and bloating were gradually resolved on the same day.

On the second day of hospitalization, she stated that the pain from insomnia last night and dizziness remained. Because EFV can increase gamma-glutamyltransferase and amylase, they also were checked (Table 1). On the next day, the patient had no headache, dizziness, or gastrointestinal disturbances. She was discharged from the hospital and advised to refer to the toxicological clinic with the prescribed laboratory tests. After 6 days of EFV overdose, the patient returned to the clinic. Physical examinations, including neurological and psychiatric, were normal. Also, all of the requested follow-up laboratory tests were in the normal range (Table 1).

Discussion

This is the first case report of acute intoxication with 12 g EFV alone in a young female. EFV, a non-nucleoside reverse transcriptase inhibitor, is used to treat HIV Type 1 infection or in combination with other nucleoside reverse transcriptase inhibitors or protease inhibitors. Our case intentionally consumed 20 tablets of EFV 600 mg as a single product, while she had no history of HIV infection. Rashmee Patil et al. reported acute liver failure in a 24-year-old Hispanic HIV-infected male who started the treatment regimen consisting of EFV/FTC/TDF two months before hospitalization. He suffered from nausea and right upper quadrant pain with a history of acute alcohol drinking a few days before admission. The authors derived that acute liver failure was associated with EFV/FTC/TDF other than alcohol and the case was recovered after stopping the medication [7]. Conversely, our case

Table 1. Patient's laboratory tests

Laboratory Tests	Results			Reference Value
Time	Day 1	Day 2	Day 6	
WBC (cells/mm^3)	6900	7900	7000	5000-10000
Neutrophil (%)	52	63	57	38-80
Hgb (g/dL)	12.9	12.9	12.5	9.5-14
Platelet (cells/mm^3)	337000	331000	294000	150000-450000
BS (mg/dL)	103	78	95	<110
Urea (mg/dL)	15	20	22	18-45
Cr (mg/dL)	0.9	0.9	0.7	0.6-1.3
Amylase (/L)	45		51	<100
SGOT (U/L)	19		17	<31
SGPT (U/L)	11		16	<31
ALP (U/L)	162		163	64-306
Na (mEq/L)	140	139	136	135-145
K (mEq/L)	4	4.5	3.9	3.5-5
PT (sec)	14.2		12	11-14
PTT (sec)	40		30	30-45
INR	1.29	1.18	1	
		VBG		
PH	7.48	7.43		7.31-7.41
PCO_2 (mmHg)	38.7	43.7		41-51
HCO_3 (mmol/L)	28.9	29		23-29
PO_2 (mmHg)	42	35		30-40
Ca (mg/dL)			9.7	8.6-10.3
GGT (U/L)	11		12.5	Up to 32
LDL (mg/dL)			99	<130
Cholesterol (mg/dL)			175	<200
HDL (mg/dL)			47	≥35
Triglyceride (mg/dL)			65	50-200

PBR

Abbreviations: WBC: White blood cell; Hgb: Hemoglobin; BS: Blood sugar; Cr: Creatinine; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic-pyruvic transaminase; PT: Prothrombin time; PTT: Partial thromboplastin time; INR: International normalized ratio; VBG: Venous blood gas; GGT: Gamma-glutamyltransferase; LDL: Low-density lipoproteins; HDL: High-density lipoprotein.

did not have previous exposure to EFV, and also no history of alcohol consumption or any other hepatotoxicity risk factors that predisposed her to liver damage. In another case series reported by Innocent Lule Segamwenge et al., four HIV-infected patients presented with remarkably increased liver aminotransferases and bilirubin led to the diagnosis of acute liver failure. All the cases were treated with the same EFV-based regimen, EFV/3TC/TDF, and recovered after discontinuation of it [8]. EFV-induced hepatotoxicity is known to be associated with chronic use with standard doses, as shown in the mentioned cases. As expected, liver function tests were normal in our case regarding the acute consumption, and also gastric irrigation in the emergency department. On the other hand, it is unknown whether a combination regimen with EFV has more likelihood of hepatotoxicity or not. However, it is recommended to monitor LFT routinely in patients receiving antiretroviral therapy [9].

Another serious concern of EFV consumption is neurotoxicity. EFV-related neurotoxicity is expected to happen within days of starting; however, its symptoms may present even after a single dose and are usually resolved after a month of therapy despite ongoing treatment [10]. One of the neuronal toxicity signs of EFV, ataxia, is related to the super-therapeutic concentration both in plasma and cerebrospinal fluid. Reports showed that the signs were improved after the discontinuation of EFV in both children and adults [11-13]. A case report of acute unintentional intoxication with 3 g of EFV in a 12-year-old HIV-negative boy showed neurotoxicity, including blurring vision, lower limb weakness, trouble walking, and tremor in upper limbs, which was gradually resolved [14]. Although the amount of EFV ingested was significantly lower in this case compared to our case, he suffered from more central nervous system toxicity which may be explained by a delay (5 days) from intoxication to admission and no prehospital treatments. In the other reported case by Talia Puzantian, a 47-year-old HIV-infected man revealed severe depression and suicidal ideation in the first few weeks of EFV addition to his treatment regimen which led to admission to the psychiatric ward and antidepressant therapy [15]. Our patient complained only of headache and dizziness which were resolved by supportive therapy. The mild signs and symptoms with no serious complications after acute ingestion of 16 g EFV may be related to high protein binding (>99%) and the small distribution volume of this drug. After 3 days and on the 6 and 30 days of follow-up she did not have any problem. Also, she did not show psychiatric symptoms on follow-up.

Conclusion

IDO is a common cause of suicidal attempts in adolescents. Although EFV is not a widely available drug, this study presented a 16-year-old non-HIV-infected girl with acute EFV intoxication. The neurotoxicity in our patient, including headache and dizziness, as the early-onset and dose-related EFV adverse effects, were successfully managed according to the early emergency department referral and gastric lavage. Another serious EFV-related adverse effect, hepatotoxicity, was not seen possibly due to the acute overdose. Finally, serious side effects of EFV were observed in HIV-infected patients who took this drug for a long time in combination with other antiretroviral drugs. Using a relatively high dose of EFV in an HIV-negative person does not expect such side effects. However, more studies are needed.

This study faced some limitations in measuring the EFV plasma concentration in which too high a concentration of this drug may increase the risk of toxicity, including neurologic toxicity. Also, measuring the drug plasma concentration could help to follow up on the patient's status.

Ethical Considerations

Compliance with ethical guidelines

Written informed consent was obtained from the patient's parents for the publication of this report. This study was conducted according to the Declaration of Helsinki principles. Also, the case report guidelines and methodology were followed in this study.

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Authors' contributions

Supervision: Navid Khosravi; Investigation, Writing original draft, and Writing review & editing: All authors; Data collection: All authors; Data analysis: Minoo Moghimi and Zahra Nekoukar.

Conflict of interest

The authors declared no conflict of interest.

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