

G. J. Wirth · J. Teuscher · J. D. Graf
C. E. Iselin

Efavirenz-induced urolithiasis

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Abstract We describe the first case of efavirenz-induced urolithiasis in a 47-year-old HIV-positive patient. Urinary obstruction led to pyelonephritis and septic shock, requiring emergency ureteral catheterisation. The subsequent clinical course was favourable, allowing the patient's discharge on day 5. A 7 mm, radio-translucent, non-crystalline, beige stone was extracted during catheterisation. Stone analysis by Fourier transform infrared spectrometry, liquid chromatography and mass spectrometry revealed a stone composed of efavirenz (EFV) metabolites M4, M5, M8 (as described by Mutlib et al. in 1999) and approximately 50% of unspecified proteins. EFV is a non-nucleoside reverse transcriptase inhibitor introduced to European markets in 1999. It is principally metabolised by cytochrome P450 3A4 and 2B6. Of the dose, 14–34% is excreted in the urine, 1% as unchanged drug. The patient had been taking 600 mg EFV per day for 3 years. As EFV-induced urolithiasis has not been reported so far, we would like to draw the attention of the medical community to this potentially severe complication.

Keywords Chemically induced kidney calculi · Efavirenz · Adverse effects · Obstructive pyelonephritis

Introduction

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for HIV therapy in the late 1990s. Its synergistic effects with other antiviral agents and its low cross-resistance have made it an essential part of modern combination therapies. The main ad-

verse effects include skin rash and nervous system symptoms [1, 2]. As EFV-induced urolithiasis has not been reported so far, we would like to draw the attention of the medical community to this potentially severe complication.

Case report

A 47-year-old man presented to the emergency department with fever, chills and 6 week history of left flank pain. He had contracted HIV 6 years previously and been treated successively with several antiretroviral drugs, including indinavir which had been stopped 3 years previously, due to lipodystrophy. His current regimen of efavirenz, abacavir and lamivudine proved effective, with a CD4 count of $543/\text{mm}^3$ [3]. Efavirenz 600 mg once daily had been introduced 3 years before.

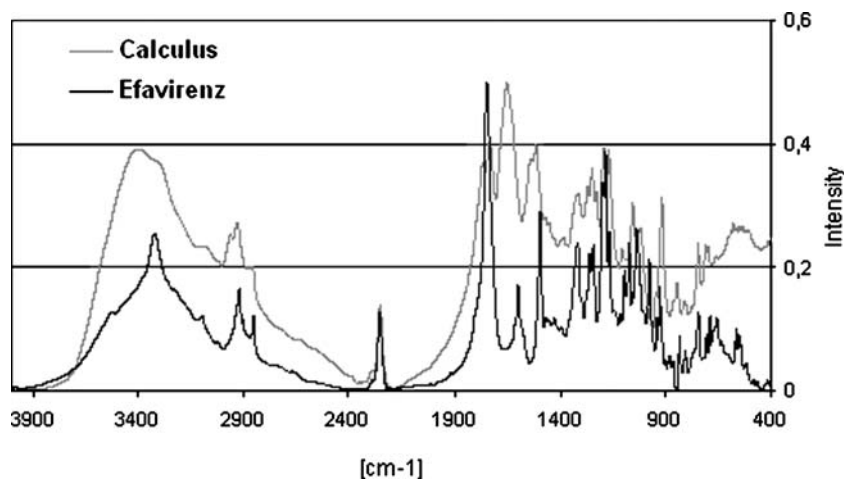


Fig. 1 Ultrasonographic image of left hydronephrosis

G. J. Wirth (✉) · C. E. Iselin
Division of Urology, Department of Surgery,
University Hospital of Geneva, Geneva, Switzerland
E-mail: jgwirth@yahoo.com

J. Teuscher · J. D. Graf
Central Laboratory of Clinical Chemistry,
University Hospital of Geneva, Geneva, Switzerland

Fig. 2 Infrared spectrograms of efavirenz (Stocrin® hard tablets) (*black*) and a probe of the calculus (*grey*). Both curves show the typical triple bond at $2,250\text{ cm}^{-1}$. Similar absorption bands were distinguished in both spectra at 3,319, 2,250, 1,737, 1,317, 1,250, 1,190, 918 and 745 cm^{-1} .



Physical examination on admission revealed 38.6°C fever, mild distress and left flank tenderness. Blood analysis was significant for a white blood cell count of $33,000/\text{mm}^3$, C-reactive protein of 180 mg/l and creatinine of $128\text{ }\mu\text{mol/l}$. Urinalysis showed 100 leucocytes, five erythrocytes and 3+ bacteria/high power field (HPF). Urine and blood cultures revealed $> 10^5$ *Escherichia coli*. Renal echography demonstrated left hydronephrosis; no obstacle was detected. (Fig. 1). No calculi were seen on plain abdominal radiography.

Pyelonephritis led to septic shock a few hours after admission, requiring emergency ureteral catheterisation and systemic cardiovascular support. A 7 mm, radio-translucent, non-crystalline, beige stone was extracted during catheterisation. Per-operative creatinine level of $208\text{ }\mu\text{mol/l}$ progressively regressed to $112\text{ }\mu\text{mol/l}$ 4 days later. The patient's subsequent clinical course was favourable, allowing his discharge on day five. Six months later, he is asymptomatic and shows no signs of recurrence. Efavirenz therapy was pursued with the same dosage.

Stone analysis by Fourier transform infrared spectrometry, liquid chromatography and mass spectrometry revealed a stone composed of the four major efavirenz metabolites and approximately 50% of unspecified proteins (Fig. 2).

Discussion

Drug-induced stones represent a highly heterogeneous entity with different aetiologies, changing epidemiology and specific clinical characteristics, accounting for 1–2% of all cases of urolithiasis [3]. HIV-positive patients are particularly at risk of developing renal stones, as their treatment frequently includes known lithogenic drugs such as indinavir and some sulfamides (i.e. sulfadiazine and sulfamethoxazole). Knowledge of drug lithogenicity can be of major help in the early treatment and prevention of urolithiasis and obstructive pyelonephritis.

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