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*Year: 2008*

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## Same patient, new stone composition: amprenavir urinary stone

Feicke, A; Rentsch, K M; Oertle, D; Strebel, R T

Feicke, A; Rentsch, K M; Oertle, D; Strebel, R T (2008). Same patient, new stone composition: amprenavir urinary stone. *Antiviral Therapy*, 13(5):733-734.

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<http://www.zora.uzh.ch>

Originally published at:  
*Antiviral Therapy* 2008, 13(5):733-734.

## Same patient, new stone composition: amprenavir urinary stone

### Abstract

We report here the first case to add amprenavir to the growing list of antiretroviral drugs associated with urinary stones. The first reported case of a nelfinavir urinary stone was reported in 2002 in a 37-year-old HIV-infected woman. In September 2007, the same female patient was referred to our department with recent onset of right flank pain and recurrent urinary tract infections. Abdominal computed tomography revealed three obstructing stones in the distal right ureter, another stone in the right renal pelvis with hydronephrosis and a stone in the left kidney. After stone retrieval, analysis of the stone by liquid chromatography with mass spectrometry revealed a stone composition of 95% unmodified amprenavir and 5% ritonavir.

## *Case report*

### **Same patient, new stone composition: Amprenavir urinary stone**

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#### *Key words*

HIV; protease inhibitors; urinary calculi

#### *Conflict of interest*

None

## **Same patient, new stone composition: Amprenavir urinary stone**

### **Abstract**

We report the first case adding amprenavir to the growing list of antiretroviral drugs associated with urinary stones. Engeler et al (2002) reported the first case of a nelfinavir urinary stone in a 37-year-old HIV infected woman. In September 2007 the same female patient was referred to our department with recent onset of right flank pain and recurrent urinary tract infections. Abdominal computed tomography revealed 3 obstructing stones in the distal right ureter, another stone in the right renal pelvis with hydronephrosis and a stone in the left kidney. After stone retrieval, the analysis of the stone by liquid chromatography with mass spectrometry revealed a stone composition of 95% of unmodified amprenavir and 5% of ritonavir.

### **Case report**

Several antiretroviral drugs such as indinavir, ritonavir, nelfinavir, saquinavir, efavirenz and atazanavir have been reported to cause urinary stones [1-5]. We report the first case adding amprenavir to the growing list of antiretroviral drugs associated with urinary stones.

Engeler et al (2002) reported the first case of a nelfinavir urinary stone in a 37-year-old HIV infected woman [2]. The medical history of this woman included intravenous drug abuse, a co-infection with hepatitis C virus (HCV) and treatment for cervical intraepithelial neoplasia. The patient was treated with antiretroviral drugs for her HIV infection for 15 years, initially with indinavir in combination with other antiretroviral drugs. Due to adverse cutaneous reactions this first regimen was discontinued and replaced by a treatment with delavirdine and nelfinavir. In 2000 she presented with two large kidney stones and underwent extracorporeal shock wave lithotripsy and percutaneous nephrolithotomy. In April 2001 a CT-scan demonstrated that the

patient was rendered stone-free. Analysis of the chemical composition of the stone revealed a content of 99% of nelfinavir and 1% of indinavir. Accordingly, the antiretroviral therapy was changed to fosamprenavir, the prodrug of amprenavir, given in combination with ritonavir and delavirdine.

In September 2007 this female patient was referred to our department with recent onset of right flank pain and recurrent urinary tract infections. The patient presented afebrile, in slightly reduced general condition with adequate hydration, stable vital signs and tender costovertebral angle on the right side. Serum levels of C-reactive protein and white blood cell count were within the normal range. Urinalysis revealed  $> 100$  leukocytes per high power field. Urine culture detected significant growth of *Aerococcus urinae* that was treated with cefuroxim according to susceptibility testing. Abdominal computed tomography revealed 3 obstructing stones in the distal right ureter (4 - 8 mm), another stone (2 x 1 cm) in the right renal pelvis with hydronephrosis and a stone in the left kidney measuring 4 mm in diameter (Figure 1). Before undergoing interventional treatment one stone had passed spontaneously. The analysis of the stone by liquid chromatography with mass spectrometry revealed a stone composition of 95% of unmodified amprenavir and 5% of ritonavir. For the analysis a few milligrams of the stone have been pulverized and suspended in methanol. After centrifugation the supernatant has been mixed with 20 mM carbonate buffer pH 9.3. Thereafter, it was directly injected into the liquid chromatography-mass spectrometry instrument (LC-MS instrument) comprising proteinase inhibitors and non-nucleoside reverse transcriptase inhibitors that are currently registered in Switzerland. Except for amprenavir and ritonavir no other peaks could be detected, demonstrating the absence of other compounds. The detection limit of the assay is about 1 ng/mg stone material. The percentage amprenavir and ritonavir has been calculated comparing the peak area of the stone material in the chromatogram with the peak area of a standard solution.

This result was confirmed subsequently by the analysis of the stone in the right renal pelvis, the fragments of which were collected after extracorporeal shock wave lithotripsy.

## **Discussion**

To our knowledge, this is the first report on a urinary stone composed of unmodified amprenavir. Amprenavir has obtained FDA and European Medicines Agency (EMA) approval in April 1999 and October 2000, respectively. Despite its long-term clinical use, amprenavir has not been associated with urinary stones so far. Amprenavir is metabolized in the liver and eliminated > 90% with faeces. Excretion of unmodified amprenavir in urine and faeces is minimal (less than 1%) [6].

In the present case, contributing pro-lithogenic patient factors were suspected. However, repeated urinalysis demonstrated a urine pH between 6 and 7 and a urine concentration constantly lower than 1.020 g/ml. Furthermore, the patient believably reported of a fluid intake of at least 1.5 to 2 liters per day. Unfortunately, so far an in depth metabolic work-up of the patient is lacking due to non-compliance of the patient. Whether this patient with concomitant HCV infection has an increased renal excretion possibly as a result of a decreased hepatic metabolism as it is described for indinavir in patients with hepatitis B or C virus infection by Malavaud et al is not known and remains speculative [7].

Although amprenavir urinary stones are an infrequent clinical problem they need to be considered in the differential diagnosis of HIV-infected patients with urinary tract symptoms.

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