Amoxycillin, a rare but possible cause of crystalluria

Giovanni B. Fogazzi, Mariadele Cantù, Lucia Saglimbeni and Michel Daudon

Research laboratory on urine of Divisione di Nefrologia, Ospedale Maggiore, IRCCS, Milano, Italy and Laboratoire de Biochimie A, Groupe Hospitalier Necker-Enfants Malades, Paris, France

Case report

Crystalluria caused by amoxycillin is a rare event that may be asymptomatic or may have severe renal implications. In January 2002 a urine sample from a 64-year-old woman which contained a large amount of unusual crystals was referred to us.

Macroscopically the urine was normal. By dipstick, pH was 5.5, relative density 1.030, and albumin and leukocyte esterase were negative. However, after centrifugation for 10 min at 400 g, removal of the supernatant urine, and resuspension of the sediment, the specimen showed a whitish and chalky appearance. The sediment, examined by phase-contrast microscopy at low (160×) and high (400×) magnifications, showed hyaline casts (++) and candida (+), squamous cells (+) and a massive crystalluria. The crystals differed remarkably from the crystals most commonly found in urine. They appeared as either (i) isolated thin and colourless needles and rods with a random distribution, and had pointed, squared, or bifid extremities, (ii) ‘bunches’, reminiscent of a broom bush, or (iii) ‘sheaves’, which were 31–236 μm wide (mean±SD on 20 crystals, 105±53 μm), and 310–527 μm long (mean±SD on 20 crystals, 406±83 μm). Under polarized light, the crystals were all highly birefringent (Figure 1).

Since these findings suggested a possible drug-induced crystalluria and the possibility of intratubular precipitation of crystals and acute renal failure [1], we immediately sought more information about the patient. We found that in the previous 2 days she had been treated with oral augmentin (amoxycillin and clavulanic acid) 1 g three times per day (corresponding to 43 mg/kg/day), for fever and diarrhoea, and that her renal function was normal (serum creatinine 0.7 mg/dl, urea 23 mg/dl). The drug was therefore stopped and 2 days later we analysed a further urine specimen. This time the centrifuged urine appeared normal. At microscopy, no crystals were found, but hyaline casts, candida and squamous cells were still present.

Infrared spectroscopy, performed by one of us (M.D.), confirmed that the crystals seen in the urine sediment were made of pure amoxycillin trihydrate (Figure 2). Thus, we concluded that our patient had had a massive and transient crystalluria caused by amoxycillin, but without any renal consequences.

What do we know about amoxycillin crystalluria?

Amoxycillin crystalluria was first noted in a 26-year-old healthy volunteer, to whom 3.0 g of the drug had been given intravenously over 20 min to investigate amoxycillin renal excretion [2]. Since then, several other cases have been reported in the literature. While some patients have only transient asymptomatic crystalluria without renal damage [2–6], others have crystalluria with gross haematuria [7], or crystalluria with gross haematuria and acute renal failure [8–12]. Crystalluria can be either macroscopic [2,5,7,9] or microscopic [2–6,8,10–12]. In the latter the crystals are as described and shown in this paper. Once amoxycillin is discontinued, the clinical abnormalities always resolve. Crystalluria disappears in 3–24 h [2,7], while gross haematuria resolves in 1–3 days [7,9,11], and acute renal failure in 3–17 days [9,11,12]. Renal failure can be non-oliguric [9,11] or oligoanuric [8,10,12], but temporary dialysis is rarely necessary [12].

Amoxycillin is rapidly absorbed in the gastrointestinal tract and excreted through the kidneys. In normal conditions, 90% of the drug is secreted by the proximal tubules, while the remaining 10% is excreted by glomerular filtration. Crystalluria is favoured by factors that reduce the solubility of the drug in the urine such as amoxycillin overdose, as observed especially in children after inadvertent ingestion of very large doses.
of the drug [7–9,11], low diuresis, or acid urine pH [2,8]. In this respect it is worth noting that our patient received a correct dose of amoxycillin but urine was very acid (pH 5.5).

It is hypothesized that haematuria and acute renal failure derive from the tubular damage and medullary congestion caused by the intrarenal precipitation of crystals [8]. However, no evidence is available, since

![Image](image_url)
none of the patients underwent renal biopsy. Another possible but less frequent mechanism is obstructive uropathy due to the massive precipitation of macroscopic crystals in the renal pelvis, as shown in the patient described by Boursas et al. [10].

Amoxicillin crystals differ strikingly from the most common urinary crystals, and this difference should prompt the microscopist to obtain additional clinical information, which may lead to the reduction of the dose or the withdrawal of the drug. However, one should also be aware that amoxicillin crystals might be similar to those caused by other drugs, for instance, ampicillin [13] or cephalaxin [14]. Therefore, a definitive identification can be obtained only with infrared spectroscopy [15] or high-performance liquid chromatography [2].

Acknowledgements. The authors are grateful to Drs Fulvia Ceccherelli and Riccardo Romano, Ospedale Maggiore di Milano, the first for providing the patient’s urine specimen for investigation, and the second for clinical information about the patient. This paper was supported by grant ‘Pippo Neglia’.

References