Urol Res (2006) 34: 58–60
DOI 10.1007/s00240-005-0002-8

CASE REPORT

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An unusual patient with kidney stones composed of 1-methyluric acid

Received: 6 May 2005 / Accepted: 20 September 2005 / Published online: 6 January 2006

Abstract An unusual case with kidney stones composed mainly of 1-methyluric acid is described. The patient, a Caucasian male of Celtic descent, reportedly drank at least eight cups of coffee per day and had a long history of rheumatoid arthritis, gouty attacks and renal colics—the latter attributed to nephrocalcinosis and analgesic nephropathy. He was treated with allopurinol. At 54 years, a bilateral nephrolithotomy was performed. Stone samples were analysed by thermogravimetry and infrared spectroscopy and reported to be 12–25% calcium oxalate, the remainder being organic uric acid-like material. Analysis of the extracts by HPLC confirmed that the organic material contained 67% of 1-methyluric acid and 33% of uric acid. Possible mechanisms leading to the precipitation of 1-methyluric acid from urine are discussed. We conclude that the high caffeine intake resulted in extremely elevated urinary concentrations of 1-methyluric acid favouring the formation of 1-methyluric acid stones.

Keywords Urolithiasis · Methyluric acid stones · Uric acid · Caffeine · Allopurinol · Analgesic nephropathy

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Introduction

We report a patient who developed kidney stones in his 30s and progressed to peritoneal dialysis continuous ambulatory peritoneal dialysis (CAPD) in his fifth decade. Although studied in 1984, this data was never published. A recent report [1], regarding identification of methylated uric acids as common admixtures in all uric acid urinary stones, prompted the presentation of this data. The objective of this report is to emphasise the possible role of methylxanthines in kidney stone disease.

Case history

The patient, a Caucasian male of Celtic descent, was a hospital theatre porter who drank at least eight cups of coffee per day during the long waiting times between operations. He had a history of rheumatoid arthritis that developed when he was 14 years for which six analgesic tablets were reportedly taken daily. He also had a history of gouty attacks and renal colics, the latter commencing at 37 years, attributed to nephrocalcinosis and analgesic nephropathy. He was treated subsequently with allopurinol (300 reduced to 100 mg/day) and at 54 years a bilateral nephrolithotomy was performed. The patient progressed to CAPD over the next year.

Methods

Nucleosides and bases in stone extracts were quantified using a Waters reversed-phase high-performance liquid chromatography (RPLC) system with in-line diode array detection. Extracts were injected onto a Hypersil ODS-1 column (250×4.6 mm, 5 μm particle size) (Hichrom Ltd.) and nucleosides and bases eluted at a flow rate of 1 ml/min using a linear gradient and monitored at 254 and 280 nm as described [2]. Ultraviolet (uv) spectra were recorded in a Perkin Elmer Spectrophotometer.

Laboratory investigations

Blood

Investigations at 56 years (when on CAPD and allopurinol), showed a plasma creatinine of 1,400 μmol/l, a uric acid of 475 μmol/l and an oxipurinol of 105 μmol/l. Erythrocyte purine salvage enzymes, adenine and hypoxanthine guanine phosphoribosyltransferase, were both within the control ranges for healthy subjects (Adenine phosphoribosyltransferase (EC 2.4.2.7) (APRT) 29, Hypoxanthine phosphoribosyltransferase (EC 2.4.2.8) (HPRT) 150 nmol/mgHb/h respectively).

Stone analysis

Stone samples from each kidney were analysed separately, initially by thermogravimetric analysis and infrared spectroscopy elsewhere and reported to be 12–25% calcium oxalate, the remainder being organic uric acid-like material, which was not uric acid (Dr. G.A. Rose, personal communication), and referred for more detailed RPLC analysis.

The uv spectrum of the crushed stone in glycine buffer was characteristic of uric acid with a maximum at 291 nm. However, incubation with uricase produced only a 33% fall in maximal absorbance. The extracts pre- and post-uricase when injected onto the RPLC system confirmed that the organic material contained 33% uric acid (completely removed by uricase incubation) and 67% of a uric acid-like component, resistant to uricase, suggesting a methylated uric acid. Millimolar standards of uric acid, 1-methyluric acid, 3-methyluric acid, 7-methyluric acid (all analytical grade from BDH) were diluted 1/31 in 0.01 mol/l HCl and the spectra recorded by RPLC from 190–310 nm at pH 2.0 and 10.0.

Results

The above standards when injected onto the RPLC system pre- and post-uricase incubation gave retention times, respectively, as follows: uric acid 8.86 min; 3-methyluric acid 11.5 min; 7-methyluric acid 12.66 min; 1-methyluric acid 14.76 min. Apart from uric acid, which was metabolised completely by uricase, there was no change in spectrum following uricase incubation for any of the methylated uric acid standards.

Injection of the pre-incubation stone extract onto the RPLC system showed only two uv absorbing peaks, the first at 8.95 min, the second at 14.76 min. Post uricase, only a single peak at 14.84 min remained, confirming that the major component of the stone was indeed 1-methyluric acid, which, like the other two methylated uric acids studied was resistant to uricase.

Discussion

The major component of the stones in this patient was 1-methyluric acid (1-MUA) which is extremely unusual, but was confirmed by irrefutable techniques. The paper by Safranow and Machoy [1] reports that methylated uric acids are found in all uric acid stones, but they are not the main component, as in this patient. Most purine-containing urinary tract stones are principally uric acid, or less frequently xanthine [3] or 2,8-dihydroxyadenine.

2,8-Dihydroxyadenine stones may also be mistaken for uric acid in routine testing [4]. However, the normal activity of APRT and HPRT in the patient's erythrocytes excluded a genetic defect in either enzyme as the basis of the stone formation.

Methylated uric acids are excreted in quantity by all subjects drinking coffee or tea; the stimulant caffeine being the major component of coffee [5]. Caffeine has at least 17 methylated degradation products [5] the principal route of 1-MUA formation from caffeine being via 1,7-dimethylxanthine and 1-methylxanthine to 1-MUA. This last step is reportedly mediated by xanthine oxidoreductase (EC 1.2.1.37) (XOR) [5]. The possibility arises that the conversion is also mediated by aldehyde oxidase (EC 1.2.3.1), but the patient described here was on allopurinol for 12 years and oxipurinol was present in the plasma, which would exclude involvement of aldehyde oxidase [6, 7].

No sample of the patient's urine was available for measurement of 1-methyluric acid concentration, but it can be assumed that during formation of the stones its output must have been high enough to make supersaturated solution (solubility of 1-MUA is 280 mg/l in water at 17.5°C [8]) and cause crystallisation. 1-MUA is the principal caffeine metabolite, constituting about 46% of all methylxanthine metabolites excreted in the urine by healthy adults. Patients taking allopurinol excrete a similar proportion of 1-MUA (48%), the excretion being even higher in patients with renal failure (69%) [9]. The latter finding could explain, at least in part, the extraordinarily high urinary output of 1-MUA in our patient with analgesic nephropathy, ingesting excessive amounts of caffeine despite taking low dose allopurinol. It may also be speculated that some individual metabolic factors e.g. high cytochrome P450 1A2 activity, catalyzing caffeine demethylation, contributed to increased 1-MUA urinary excretion, which could significantly exceed the excretion of uric acid (UA), as in this case [5].

Both 1-MUA and UA are poorly soluble in aqueous solutions, especially at low pH. Thus, in a urine supersaturated with both 1-MUA (major component) and UA (minor component), the compounds could co-precipitate forming a solid solution of UA in 1-MUA, the reverse of the phenomenon described in the paper cited [1] where 1-MUA (and other methyluric acids and methylxanthines) formed solid solutions in uric acid stones, but were the minor component. The necessary

condition for two or more organic compounds to form a solid solution is the similarity of shape and size of their molecules. This condition is fulfilled by UA and 1-MUA [1].

It appears that 1-methyluric acid stone formation in this instance was an occupational hazard resulting from long waiting times between delivery and collection of patients, which provided the necessity/opportunity for a very high caffeine intake. Against this argument is the fact that many people are avid coffee consumers and do not form stones. The pre-existing renal disease in this case, due to excessive analgesic intake would increase the percentage of excreted 1-MUA. Another contributing factor is the finding that methylated uric acids, unlike uric acid, are cleared readily by the kidney, plasma levels being low to undetectable. Thus a high caffeine intake would result in extremely elevated urinary concentrations favouring the formation of the 1-methyluric acid stones under appropriate conditions, as reported here.

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