REVIEW ARTICLE

Drugs 2004; 64 (3): 245-275
0012-6667/04/0003-0245/$34.00/0

Drug-Induced Renal Calculi
Epidemiology, Prevention and Management

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Contents

Abstract

Drug-induced calculi represent 1–2% of all renal calculi. The drugs reported to produce calculi formation may be divided into two groups.

The first one includes poorly soluble drugs with high urine excretion that favours crystallisation in the urine. Among poorly soluble molecules, triamterene was the leading cause of drug-containing urinary calculi in the 1970s, and it is still currently responsible for a significant number of calculi. In the last decade, drugs used for the treatment of HIV-infected patients, namely indinavir and sulfadiazine, have become the most frequent cause of drug-containing urinary calculi. Besides these drugs, about twenty other molecules may induce nephrolithiasis in patients receiving long-term treatment or high doses. Calculi analysis by physical methods, including infrared spectroscopy or x-ray diffraction, is needed to demonstrate the presence of the drug or its metabolites within the calculi.

The second group includes drugs that provoke urinary calculi as a consequence of their metabolic effects. Here, diagnosis relies on careful clinical inquiry because physical methods are ineffective to differentiate between urinary calculi induced by the metabolic effects of a drug and common metabolic calculi. The incidence of such calculi, especially those resulting from calcium/vitamin D supplementation, is probably underestimated.

Although drug-induced urinary calculi most often complicate high-dose, long-duration drug treatments, there also exist specific patient risk factors in relation to urine pH, urine output and other parameters, which provide a basis for preventive or curative treatment of calculi.

Better awareness of the possible occurrence of lithogenic complications, preventive measures based on drug solubility characteristics and close surveillance of patients on long-term treatment with drugs with lithogenic potential, especially those with a history of urolithiasis, should reduce the incidence of drug-induced nephrolithiasis.

Drug-induced renal calculi (kidney stones) represent 1–2% of the total number of renal calculi analysed in specialised laboratories. Historically, sulfonamides were the first drugs implicated in renal calculi formation and acute renal failure episodes early after their use in humans. A number of reports were published on sulfonamides and renal disorders.[1-5] For years thereafter, only sporadic observations of renal calculi induced by various drugs have been reported in the literature. It was not until the early 1980s that the notion of drug-induced nephrolithiasis was individualised and conceptualised within the wider concept of drug-induced renal disease.[6-12] In this article, the diagnosis, epidemiology, prevention and management of drug-induced renal calculi are reviewed.

Two main mechanisms are involved in the formation of drug-induced renal calculi: (i) the drug and/or its metabolites are total or partial components of the calculi; and (ii) the drug induces the formation of calculi through its metabolic action by interfering with calcium oxalate or purine metabolism.[11-13] In both cases, a lithogenic substance may deposit on renal calculi already present. Therefore, patients with a history or presence of renal calculi seem to be more exposed to the risk of drug-induced renal calculi.

1. Diagnosis of Drug-Induced Nephrolithiasis

Aetiological inquiry on the patient's medical history, coexisting comorbidity and drug intake is essential to establish the causal link between drug

consumption and formation of renal calculi.[7,12] Onset of renal colic soon after introduction of a drug in a patient without history of renal calculi should immediately alert to the possibility of drug-induced calculi. However, the problem is more difficult if the patient receives several potentially lithogenic drugs simultaneously, or when nephrolithiasis becomes evident after several years of treatment with the same drug or even after the drug has been discontinued.[14]

Most, if not all, drug-containing calculi are radiolucent on plain abdominal x-ray, but are detectable by echography. Adequate analysis of calculi by physical methods able to recognise all organic compounds, such as x-ray diffraction,[15] mass spectroscopy or, more easily, infrared spectroscopy associated with optic examination,[16] is essential to identify drug-containing renal calculi, according to the specific spectra of the drugs or metabolites.[17] In patients with acute renal failure, investigation for the presence and composition of crystalluria may be very informative in emergency situations when no renal calculus is available for analysis.[18-21]

Drug compounds or metabolites that crystallise in urine are listed in table I.

2. Risk Factors for Drug-Induced Renal Calculi Formation

Obviously, only a limited proportion of patients treated with widely used drugs such as triamterene or sulfonamides develop crystalluria, renal colic or acute renal failure due to tubular obstruction by drug crystals. This suggests that the formation of drug-induced calculi involves an interplay of risk factors specific for the implicated drug, some of which depend on the drug itself and others that relate to the patient.[12,13,22]

Individual risk factors related to the patient are listed in table II and risk factors related to the drugs are listed in table III.

In addition, specific diseases should alert to the possibility of drug-induced nephrolithiasis. For instance, gastrointestinal diseases suggest use of antacids or of sulfonamide derivatives; gout or hyperuricaemia, use of uricosurics; arthrosis or other pain, use of analgesic or anti-inflammatory agents; urinary tract infection, use of urinary antibacterial agents; hypertension, use of triamterene. Treatment of HIV infection relies on protease inhibitors and/or other antiviral drugs, and also on treatment of bacterial and opportunistic infections using drugs such as sulfadiazine and sulfamethoxazole. Certain drugs within each of these classes have the potential to cause formation of renal calculi (see table I for examples).

3. Epidemiology

Very few studies have examined the part taken by drug-induced renal calculi within the spectrum of renal calculi disease. Most studies refer to large series of calculi analysed in specialised laboratories. Therefore, these studies are only able to identify renal calculi within which the drug or its metabolites are present, to a greater or lesser extent, as calculi components. Indeed, because drug-induced metabolic calculi (see section 5) do not differ in appearance from common metabolic calculi, they usually cannot be identified on the sole basis of calculi analysis alone without knowledge of the pathological context of the patient. Therefore, the true prevalence of drug-induced renal calculi is likely to be underestimated in most studies. However, in some cases, changes in urine biochemistry induced by the drug may provoke crystallisation of metabolic compounds with an unusual morphology, which may draw attention to the possibility that there are peculiar conditions for the renal calculi formation.[23]

The first large-scale epidemiological study of drug-induced nephrolithiasis was presented in 1980 by Ettinger et al.[24] The authors reported that 0.4% of 50 000 renal calculi analysed over a 6-month period in the US contained triamterene, but they did not provide data as to possible other types of drug-induced calculi. In 1986, Asper[25] observed an incidence of 0.1% for drug-containing urinary calculi among a series of 14 165 calculi analysed between 1982 and 1985 in Switzerland. Rapado et al.,[12] in Spain, analysed 1500 renal calculi from 1981 to 1985; 12 (0.8%) were composed of drugs to some extent.[12] During the period 1975 to 1985, Réveil-

Table I. Drugs which may crystallise in urine

Drug	Crystalline form in urine and/or calculi
Antibacterial drugs	
Sulfonamides	
Sulfadiazine	N-acetylsulfadiazine, sulfadiazine
Sulfaguanidine	N-acetylsulfaguanidine, N,N-diacetylsulfaguanidine
Sulfamethoxazole	N-acetylsulfamethoxazole hydrochloride
Sulfaperin	N-acetylsulfaperin
Sulfafurazole (sulfisoxazole)	N-acetylsufisoxazole
Aminopenicillins	
Amoxicillin	Amoxicillin trihydrate
Ampicillin	Ampicillin trihydrate
Cephalosporins	
Ceftriaxone	Calcium ceftriaxonate
Quinolones	
Ciprofloxacin	Magnesium ciprofloxacin salt
Flumequine	Flumequine
Norfloxacin	Magnesium norfloxacin salt
Oxolinic acid	Oxolinic acid
Pipemidic acid	Pipemidic acid metabolite[a]
Furanes	
Nitrofurantoin	Nitrofurantoin
Pyridines	
Phenazopyridin	Hydroxyphenazopyridin sulfate and other metabolites
Protease inhibitors	
Indinavir (indinavir sulfate)	Indinavir monohydrate
Nelfinavir	Nelfinavir
Analgesics	
Amino-4-quinoleines	
Glafenine	Glafenic acid and hydroxyglafenic acids
Antrafenine	Antrafenic acid
Floctafenine	Floctafenic acid glucuronide
Antihypertensive agents	
Pteridines	
Triamterene	Triamterene, hydroxy-4′-triamterene sulfate, hydroxy-4′-triamterene and glucuronide metabolites
Antacids	
Silicium derivatives	
Magnesium trisilicate	Amorphous silica
Colloid silica	Amorphous silica
Aluminium derivatives	
Aluminium hydroxide	Aluminium magnesium potassium urate
Other drugs	
Primidone	Primidone[a]
Methotrexate	Methotrexate and 7-hydroxy-methotrexate[a]
Guaifenesin	Calcium salt of β-(2-methoxyphenoxy)lactic acid
Allopurinol	Oxypurinol
Sulfasalazine	N-acetylsulfapyridine

a Observed as crystals in urine but not yet reported in renal calculi.

laud and Daudon[11] found that 58 of 4000 urinary calculi (1.45%) contained drugs. Triamterene was the most often encountered substance in both of the latter studies.

Our further experience documents the changes in the epidemiology of drug-induced nephrolithiasis over time. A total of 37 621 urinary calculi referred from all parts of the country were examined at our laboratory (Laboratoire Cristal, Paris, France) from 1975 to 2002 by Fourier transform infrared spectroscopy (FTIR). The evolution of the overall proportion of calculi containing drugs or metabolites, and of the relative frequency of implicated drugs, is shown in table IV. The overall prevalence of drug-containing calculi was 1%. The leading causative molecules identified were glafenine and triamterene during period I (1977–86), triamterene and sulfonamides in period II (1987–96) and indinavir and triamterene in period III (1997–2002).

4. Drug-Containing Renal Calculi

4.1 Triamterene-Induced Renal Calculi

The potassium-sparing diuretic triamterene is often prescribed for the treatment of hypertensive disorders. It is commonly administered in association with a thiazide diuretic in order to minimise the risk of hypokalaemia. A popular combination in the US is Dyazide®[1], which contains 50mg of triamterene and 25mg of hydrochlorothiazide per tablet.

4.1.1 Epidemiological Data

Although in wide use since 1961, it was only in 1979 that Ettinger et al.[26] reported the first case of triamterene-associated nephrolithiasis, in a 52-year-old woman treated for hypertension with hydrochlorothiazide and triamterene (300 then 350 mg/day), who passed nearly 50 small mustard-coloured renal calculi (figure 1) until triamterene was discontinued. Similar cases were reported soon after in the US by Socolow,[27] in a patient who previously had uric acid urolithiasis, and in France by Baudin and Rodrigue[28] in a patient with a history of calcium oxalate calculi. Thereafter, several cases on triamterene-containing urinary calculi were reported.[29-31]

As noted in the previous section, in 1980 Ettinger et al.[24] identified triamterene in 181 of about 50 000 renal calculi from US patients referred for analysis at Herring Laboratory, a prevalence of 0.4%.[24] In 1982, in France, we found triamterene in 4 of 1000 renal calculi analysed by infrared spectroscopy at our laboratory (Laboratoire Cristal), also a prevalence of 0.4%,[31] and Moesch et al.[32] identified triamterene in 4 of 1000 renal calculi referred to their laboratory, again a prevalence of 0.4%. Among the 181 patients reported by Ettinger et al.,[24] a history of previous oxalate or uric acid calculi was frequently found, more often in those whose calculi contained minor amounts of triamterene than in those with calculi predominantly made of triamterene (35% vs 19%). Carey et al.[33] similarly observed that patients with a history of nephrolithiasis were more prone to form renal calculi while on triamterene therapy than those devoid of previous calculi disease (35% vs 4%). Such observations suggest that the development of drug-induced calculi is favoured by previous calculi, and even more so by present calculi *in situ* that offer physical support for the deposition of triamterene and its metabolites.

The incidence of triamterene-induced renal calculi has markedly decreased over the past decade in our experience, as shown in table IV. The reasons for this decrease are probably that the medical community is better informed regarding the lithogenic effects of triamterene,[34-36] and that alternatives to

Table II. Patient-dependent risk factors for drug-induced urinary calculi

Personal or family history of nephrolithiasis
Pre-existing calculi
Urinary stasis (malformative uropathy, prostatic hypertrophy)
Underlying lithogenic metabolic abnormalities (e.g. hypercalciuria, hypocitraturia)
Detoxification enzyme pattern
Abnormally low or high urine pH
Urinary tract infection
Low urine output
Environmental factors (e.g. hot temperature)

1 The use of tradenames is for product identification purposes only and does not imply endorsement.

Table III. Drug-specific risk factors for drug-induced urinary calculi

High daily dose of drug
Long-standing treatment
High urinary excretion of the drug and/or its metabolites
Low aqueous solubility of the drug and/or its metabolites
Short half-life of the drug, inducing concentration peaks in urine
Concomitant therapy that causes changes in the pharmacokinetics or metabolism of the drug
Size and morphology of drug crystals

this antihypertensive drug have been developed in recent years.

In the report of Ettinger et al.[24] of 181 triamterene-containing renal calculi examined by infrared spectroscopy, 36% of calculi were composed mainly or entirely of triamterene, whereas the remainder showed minor amounts of triamterene with variable amounts of usual constituents such as calcium oxalate or uric acid and proteins. In our series (table IV), only 25% of triamterene-associated renal calculi observed in 75 patients were made exclusively of triamterene admixed with some proportion of proteins, whereas in the other cases triamterene was associated with usual constituents such as calcium oxalate or phosphate and/or uric acid in variable amounts. Triamterene was present in the nucleus of the calculi in 72% of patients.

Chromatographic data showed the drug moiety of triamterene-associated calculi to be made of a mixture of unchanged triamterene and its metabolites, hydroxy-4′-triamterene sulphate and, less frequently, hydroxy-4′-triamterene in its free form.[31,37] The relative proportion of these three compounds widely varied between patients, with hydroxy-4′-triamterene sulphate often being the major component, as it is the main metabolite excreted in urine.[31] In some patients, the drug moiety was nearly pure hydroxy-4′-triamterene sulphate, thus modifying significantly the infrared spectral pattern (figure 1).[17] Recently, Sabot et al.[38] reported the presence of other triamterene metabolites in some urinary calculi.

4.1.2 Risk Factors for Triamterene-Induced Calculi

Composition of the triamterene-associated calculi is in keeping with the pharmacokinetics and solubility of triamterene and its main metabolites. After oral administration of the drug, 30–70% of the dose is absorbed, with the excretion peak of the drug and its phenolic metabolite hydroxy-4′-triamterene occurring within 2–3 hours.[39] The solubility of triamterene and hydroxy-4′-triamterene is low, at about 20 mg/L, and this is poorly affected by urine pH.[36] The sulphate metabolite is somewhat more soluble than triamterene itself[40] but, because it constitutes the most abundant metabolite in urine, its concentration peak is often high, so that urine is often supersaturated for that metabolite.

The high degree of urinary excretion and poor solubility of the drug result in the presence of crystals of triamterene and metabolites in the urine 2–4 hours after ingestion in about half of patients and healthy volunteers taking the drug.[41] Animal studies showed that birefringent crystals and casts form within the collecting ducts of the kidney.[42] These findings are in keeping with an observation of acute renal failure associated with intracellular deposition of triamterene crystals within distal tubular epithelial cells as reported by Farge et al.[43] after ingestion of a massive dose of Dyazide®, or with tubular obstruction by crystals as reported by Roy et al.[44] However, despite the frequent occurrence of crystalluria in triamterene-treated patients, only a few develop urinary calculi; the incidence of affected patients ranges between 1 of 1500 and 1 of 2000 treated patients.[24,45] Thus, individual predisposing factors are likely to play a role.[35]

Risk factors for the formation of triamterene-induced calculi have been investigated. No differences in the absorption and excretion of triamterene were found between patients who developed urinary calculi and controls who did not in studies by Carey et al.[33] and by Ettinger.[46] However, analysis of clinical reports shows that two factors emerge as favouring triamterene-associated calculi formation. The first factor is drug posology. Daily doses up to 100 mg/day were rarely associated with calculi formation, whereas triamterene-associated calculi were mostly found in patients receiving a higher daily dose (150 mg/day in France, 200 mg/day in the US). The second factor is urine pH. Fairley et al.[41] showed that tubular casts containing triamterene

crystals were consistently found in the urine of patients when pH was <6.0 but were absent in alkaline urine. Kau[47] observed that tubular reabsorption of triamterene is increased in the setting of an alkaline urine, whereas triamterene excretion is increased in acidic urine. Thus, the lower incidence of triamterene crystalluria in alkaline urine is more likely to be explained by this reduced excretion than by the slight increase in solubility of triamterene and metabolites which occurs in alkaline urine.[48] Of note, low urine pH also promotes the formation of uric acid crystals and calculi. This may explain the abnormally high proportion of triamterene-containing renal calculi that simultaneously contain uric acid, as reported by Ettinger et al.[24] and as observed in our patients.

Triamterene may induce formation of triamterene-containing renal calculi in three ways.

1. Homogeneous nucleation of calculi made almost entirely of triamterene or its metabolites, especially hydroxy-4′-triamterene sulphate, because of high urine supersaturation. In this respect, enhanced sulfoconjugation of hydroxy-4′-triamterene in patients receiving a high intake of inorganic sulphate, through abundant consumption of animal proteins and/or of sulphate-rich drinking water, may be a favouring factor for both acidic urine and high hydroxy-4′-triamterene sulphate excretion.

2. Heterogeneous nucleation of other crystals, such as calcium oxalate or phosphate, or uric acid, on triamterene crystals. This hypothesis is substantiated by the observation of a nucleus made of triamterene surrounded by layers of calcium oxalate or uric acid in a rather high proportion of triamterene-containing renal calculi as observed by Ettinger et al.[24] and us.[49] In addition, White and Nancollas[50] showed that addition of triamterene seeds induces the heterogeneous nucleation and growth of calcium oxalate monohydrate crystals, although Werness et al.[51] failed to observe such phenomenon.

3. Accretion of triamterene crystals onto existing calcium or uric acid calculi. Such a mechanism is substantiated by the frequent development of triamterene-containing calculi in patients with a history of calcium or uric acid calculi. In addition, Werness et al.[51] have shown that triamterene and its metabolites are assimilated into existing calculi by adsorption on the protein matrix common to most renal calculi whatever the mechanism(s) involved.

In all cases, low urine volume acts as a common favouring factor for development of the urinary calculi.

Although not strictly speaking related to nephrolithiasis, another renal complication of triamterene therapy is worth mentioning.[48] Acute, most often reversible, renal failure has been reported in several patients receiving a combination of thiazide diure-

Table IV. Evolution over time of the overall proportion of drug-containing calculi, and distribution of the most frequently identified molecules, in an analysis of 37 621 urinary calculi over the period 1977–2002 (Laboratoire Cristal, Paris, France)

	Period I (1977–86)	Period II (1987–96)	Period III (1997–2002)
Total no. of stones analysed	4086	16 251	17 284
No. of drug-containing calculi (% of total)[a]	56 (1.4)	120 (0.7)	196 (1.1)
Frequency of molecules identified (% of total drug-containing calculi for time period)			
Indinavir monohydrate	0 (0)	17 (14.2)	119 (60.7)
Triamterene and metabolites	18 (32.1)	33 (27.5)	24 (12.2)
Sulfadiazine and/or N-acetyl-sulfadiazine	2 (3.6)	19 (15.8)	20 (10.2)
Glafenic acids	21 (37.5)	16 (13.3)	3 (1.5)
Opaline silica	2 (3.6)	18 (15)	13 (6.6)
Phenazopyridine metabolites	4 (7.1)	1 (0.8)	1 (0.5)
Oxypurinol (+ xanthine)	3 (5.4)	2 (1.7)	0 (0)
Calcium ceftriaxonate	0 (0)	0 (0)	6 (3.1)
Amoxicillin trihydrate	0 (0)	4 (3.3)	5 (2.6)
Others	6 (10.7)	7 (5.8)	5 (2.6)

a Total number of drug-containing calculi for the entire time period was 372 (1%).

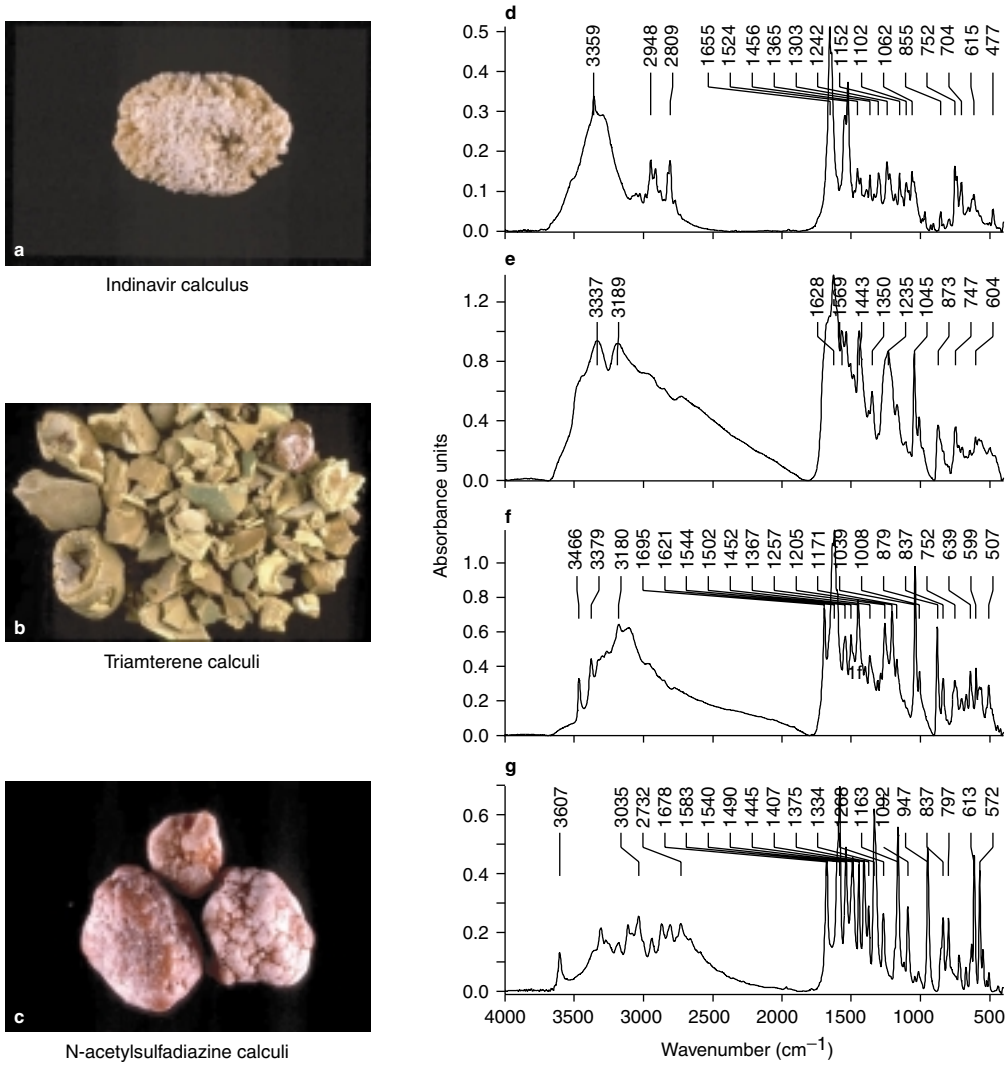


Fig. 1. Photographs of drug-containing renal calculi: (**a**) indinavir monohydrate; (**b**) triamterene; (**c**) N-acetylsulfadiazine. Infrared spectra of drug-containing calculi: (**d**) indinavir monohydrate; (**e** and **f**) two typical spectra of triamterene-containing stones: (**e**) mixture of triamterene and metabolites with proteins; (**f**) hydroxyl-4′-triamterene sulphate; and (**g**) N-acetylsulfadiazine.

tics and triamterene for the treatment of oedematous conditions.[52] This complication was mostly observed in patients with cardiac failure and depressed renal blood flow who received NSAIDs[43,53,54] or captopril.[55]

4.1.3 Preventative Measures

Preventative measures derive from the above-mentioned considerations. Specific risk factors for triamterene-induced urinary calculi are history of uric acid urolithiasis, hyperuricosuria and low urinary pH.[13] Triamterene therapy should be avoided in patients with a history of nephrolithiasis, especially uric acid lithiasis, which suggests the coexistence of permanently acidic urine. Patients treated with a combination of thiazide diuretics and triamterene, especially elderly patients with suspected renal hypoperfusion, should be carefully followed. Concom-

itant use of NSAIDs and of the triamterene-thiazide diuretic combination should be avoided.

As suggested by the studies of Spence and coworkers,[56] amiloride, which has the same properties as triamterene but which does not provoke an abnormal urine sediment, should be preferred to triamterene in patients with known risk factors, and substituted for triamterene in patients who develop renal complications while on triamterene therapy.

4.2 Protease Inhibitor-Induced Crystals and Renal Calculi

4.2.1 Indinavir

Because indinavir is currently the major cause of drug-induced nephrolithiasis, it deserves a comprehensive description.

The introduction of protease inhibitors was a major advance in the treatment of HIV infection. The triple association of protease inhibitors with non-nucleoside and nucleoside reverse transcriptase inhibitors now constitutes the basis of care for many HIV-infected patients.[57,58] Among protease inhibitors currently licensed (indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and amprenavir), indinavir (Crixivan®) is commonly prescribed because it combines good antiviral efficacy and fair gastrointestinal tolerability, despite its known risk of crystalluria and nephrolithiasis. Shortly after its introduction in 1995 in the US and in 1996 in Europe, indinavir was associated with the frequent occurrence of radiolucent renal calculi. In our experience, indinavir has replaced triamterene as the leading cause of drug-associated nephrolithiasis over the past 5 years (table IV).

Epidemiological Data

The initial product monograph for indinavir mentioned an incidence of urinary calculi of 4%.[59,60] It soon became apparent that the incidence of nephrolithiasis in indinavir-treated patients was much higher, with 7.3% of 781 patients for Herman et al.,[61] 8% of 240 patients for Kopp et al.,[62] 9% of 155 patients for Hermieu et al.,[63] 9.4% of 309 patients for Piroth et al.,[64] 12.2% of 106 patients for Boubaker et al.[65] and 12.4% of 105 patients for Reiter et al.[66] The incidence was as high as 36% in a cohort of 33 patients followed over 3 years by Gulick et al.,[67] and 43.2% in a series of 155 patients reported by Saltel et al.[68]

Clinical presentation of indinavir-associated nephrolithiasis includes typical renal colic,[61] flank or loin pain, or dysuria.[61,62,69] Pure indinavir calculi are totally radiolucent on plain abdominal radiograph, and also on computed tomography (CT).[70-72] They can only be visualised by echography (often indirectly by the aspect of pyelocaliceal dilation), by intravenous pyelography or by contrast-enhanced CT.[73,74] The latter may reveal filling defects within the renal parenchyma.[75] A reversible, transient increase in serum creatinine level is often observed during episodes of renal colic.[61,76]

In the majority of patients, indinavir-containing calculi are spontaneously passed in the urine with the help of conservative treatment.[62] In a minority of patients, urological intervention may be required, usually in the form of ureteric stenting or ureteroscopy.[70-72,77] Extracorporeal shock-wave lithotripsy (ESWL) is often ineffective because of the proteinaceous loose structure of indinavir calculi,[70] but may be indicated in patients with calcium-containing renal calculi.[62]

Usually, clinical symptoms resolve and serum creatinine levels return to normal values after spontaneous passage or extraction of obstructive urinary calculi, but recurrence is frequent if active prophylactic measures are not maintained in the long term.[78,79] In some patients renal function has remained abnormal after indinavir discontinuation.[80-82]

Besides calculi episodes, other more severe renal complications relating to indinavir crystal formation may occur. Several cases of acute, non-oliguric or oligo-anuric renal failure in the absence of obstructive indinavir calculi have been reported, with elevation of the serum creatinine level up to 7.1 mg/dL;[80-87] the renal failure was usually reversible after indinavir withdrawal. Renal biopsy showed interstitial nephritis with presence of indinavir crystals in cortical and medullary collecting ducts.[80,84] A progressive renal failure, marked by a slow (usu-

ally moderate) increase in serum creatinine level has been reported in 18.6% of 106 indinavir-treated patients by Boubaker et al.,[65] and in 18% of 72 patients by Sarcletti et al.[88] This also resolved after drug discontinuation. In the latter study, increased serum creatinine levels were mostly found in women, and were associated with aseptic pyuria and microhaematuria; renal biopsy performed in three patients revealed tubulointerstitial nephritis with indinavir crystals in collecting ducts. Other authors have also reported cases of sterile pyuria attributed to indinavir-induced nephritis.[89,90]

Treatment with indinavir started in France in April 1996. We first reported the composition of urinary calculi in indinavir-treated patients in July 1997.[91] Between 1996 and 2002, 157 urinary calculi from patients treated with indinavir were referred to our laboratory, of which 136 contained indinavir, thus representing 0.74% of the 18 460 urinary calculi examined during the same period. All calculi were analysed using stereomicroscopy and FTIR.[16] Indinavir-containing calculi all had a similar morphology (figure 1). They ranged from 2–6mm in diameter, with a beige, rough surface. FTIR spectra revealed that indinavir was present in the form of indinavir monohydrate, the proportion of which ranged between 3% and 97%. Mass spectrometry confirmed the presence of indinavir base as identified by the FTIR spectrum (figure 1).[91] Indinavir was the only constituent (admixed with some proteins) in 67% of calculi, and was present in 93% of nuclei. Metabolic compounds, such as calcium oxalate and/or phosphate, were present in about 30% of calculi. Four calculi also contained amounts of N-acetylsulfadiazine, and one radiolucent calculus without indinavir was made of pure uric acid in a patient who received urine-acidifying therapy for the prevention of indinavir-containing calculi recurrence.

Indinavir Crystalluria

The frequent occurrence of indinavir crystalluria and nephrolithiasis in indinavir-treated patients is explained by the physicochemical properties and pharmacokinetics of the drug. The commonly used schedule consists of oral indinavir 800mg every 8 hours, associated with a fluid intake of at least 1500 mL/day as recommended in the fabricant notice. Indinavir given by mouth is rapidly absorbed and about 20% of the ingested dose is excreted in urine within 24 hours, including 11% in the form of the unchanged drug and the remaining as metabolites.[92] Indinavir solubility is highly pH-dependent. In aqueous solutions, indinavir solubility is ≥300 mg/L at pH below 5.0, 35 mg/L at pH 6.0 and only 20 mg/L at pH 7.0.[93] On the basis of the pharmacokinetics of indinavir,[94] it may be predicted that urinary concentration of the drug 3 hours after an oral 800mg dose should be about 200–300 mg/L if daily urine output is about 1500mL.[91] At the usual urine pH, such concentrations will often be at the limit of solubility.

Indeed, crystalluria is a very frequent finding in indinavir-treated patients. Indinavir crystalluria was found in 20% of 142 patients treated with indinavir in a study by Kopp et al.[62] All 19 patients who had urological symptoms while receiving indinavir were found to have crystalluria and/or nephrolithiasis. However, this study failed to find any relationships between crystalluria and the risk of developing indinavir-containing calculi. The incidence of urolithiasis was found to be 12.4% in 105 indinavir-treated patients in a study by Reiter et al.;[66] the urine of all patients who formed calculi was subsequently found to contain indinavir crystals. The incidence of crystalluria in indinavir-treated patients was higher in some other studies: 31% of 308 freshly voided urine specimens from 168 indinavir-treated patients in an analysis by Hortin et al.,[95] and 44% of 208 patients in an analysis by Rickerts et al.[96] Gagnon et al.[97] observed the presence of crystalluria at some time during follow up in 67% of 54 indinavir-treated patients whose urine specimens were monitored at monthly intervals for 1 year, and in about 25% of samples at each point test. We performed a prospective study on 138 patients treated with indinavir from January 1997 until December 1998 at Necker Hospital (Paris, France). Indinavir crystals were found in 34% of urine samples taken within 3 hours after the first indinavir morning dose of 800mg.[98] Crystals were present in 56% of sam-

ples with a pH ≥6.5, compared with 22% when pH was <5.5,[99] indicating a clear pH-dependence of crystalluria (figure 2). Patients who formed calculi and patients with asymptomatic indinavir crystalluria were then recommended to have a high fluid intake after each oral dose of indinavir. Serial urine specimens obtained in 44 patients evidenced a significant decrease in indinavir crystalluria in 67% of cases.[98]

Risk Factors for Indinavir-Induced Renal Complications

Risk factors for the development of indinavir-associated renal complications have been reviewed by Herman et al.[61] and by Famularo et al.[100] The basic factor is the reduced solubility of indinavir at urine pH >5.5, which was confirmed in several clinical studies[72,95-98] and in our experience. Another factor that may explain the high frequency of clinical symptoms is the shape of the indinavir crystals. Typically, indinavir monohydrate crystallises as very large needle-shaped crystals (100–500μm)[101] which form large plates with parallel striations (figure 3), or grouped as radiating aggregates.[21,62,99] Such crystals may easily provoke obstruction of renal tubules, calculi formation and dysfunction of the kidney. Additional clinical factors may enhance the risk of indinavir-associated urolithiasis.

- Episodes of dehydration provoked by a hot temperature,[78,79] or by severe diarrhoea which is not uncommon in AIDS patients.[100]

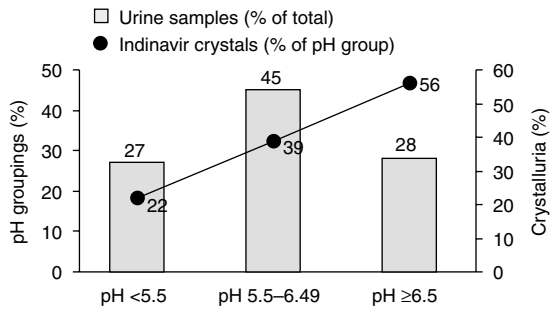


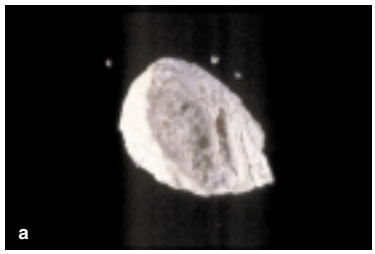
Fig. 2. Occurrence of indinavir crystalluria according to urine pH value. Bars represent the proportion of urine samples found for every pH range (left axis). The full line represents the percentage of urine samples in each pH group that contained indinavir crystals (right axis).

- Concomitant administration of other drugs such as aciclovir, as mentioned by Herman et al.[61] and Hanabusa et al.,[102] or co-trimoxazole, as reported by Boubaker et al.[65]
- Co-infection with hepatitis C virus (HCV) and HIV, as has been seen in patients with or without haemophilia.[103-105] The most likely explanation for the frequent occurrence of indinavir crystalluria in such patients is that latent or overt hepatic insufficiency resulting from HCV infection results in reduced hepatic indinavir catabolism and increased renal excretion.[105]
- High plasma concentrations of indinavir, which may result from blood volume depletion, from pharmacodynamic interactions between indinavir and other drugs as suggested by Dieleman et al.,[106] from use of the standard posology in patients with low body mass as observed by Boubaker et al.,[65] from high indinavir dose/body mass index ratio as reported by Meraviglia et al.,[107] or from administration of indinavir at 1200mg twice daily, as observed in the case reported by Famularo et al.[100]

To exemplify the last point, Dieleman et al.[108] compared indinavir plasma concentrations in 15 indinavir-treated patients presenting with urological complaints (symptomatic group) with those in 14 patients who received indinavir without urological complaints (control group). They found that 93% of the symptomatic group had plasma indinavir concentrations above the mean value found in the control group. Eighty percent of the symptomatic patients had a concentration above the upper 95% confidence limit. All patients in both groups received indinavir 800mg three times daily. The indinavir dose was reduced to 600mg three times a day in six of the patients with urological complaints; repeat measurements of their indinavir plasma concentrations then found values within the 95% confidence interval around the mean value of the control group. All six patients remained asymptomatic without loss of efficacy of the drug.[108]

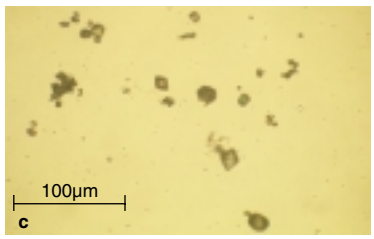
Management and Preventative Measures

The treatment of symptomatic calculi relies primarily on conservative measures, including in-



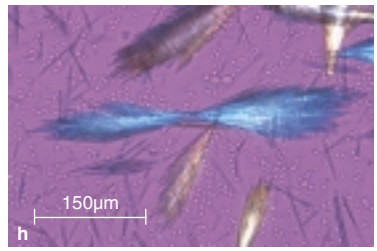
Amorphous silica stone

Amoxicillin calculus

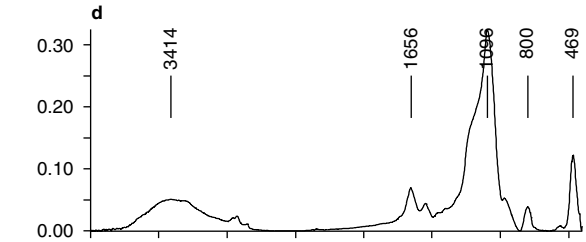


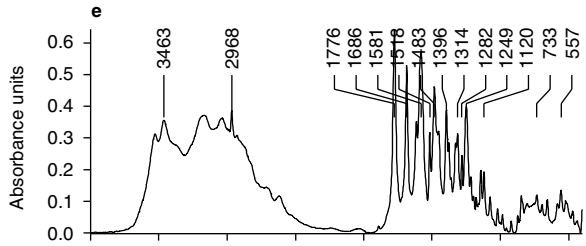
N-acetylsulfamethoxazole hydrochloride crystals

Indinavir crystals



Amoxicillin crystals





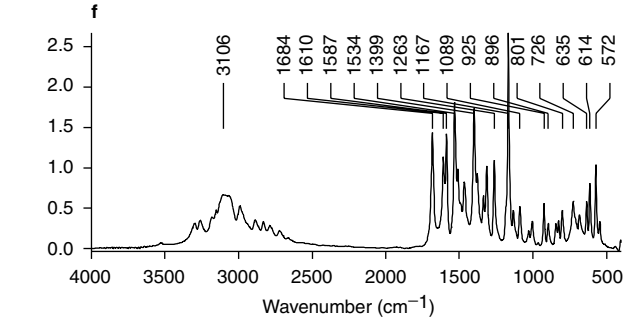


Fig. 3. Photographs of drug-containing urinary calculi and crystals: (**a**) silica; (**b**) amoxicillin; (**c**) N-acetylsulfamethoxazole hydrochloride crystals in urine. Infrared spectra of drug-containing calculi: (**d**) amorphous silica admixed with proteins; (**e**) amoxicillin trihydrate; (**f**) N-acetylsulfamethoxazole hydrochloride. View under polarising light of: (**g**) typical striated plate of indinavir monohydrate crystals; (**h**) needle-shaped aggregated crystals of amoxicillin trihydrate.

travascular volume expansion and analgesic treatment, because most indinavir calculi pass spontaneously in the urine.[109] Temporary discontinuation of indinavir is often prescribed. In patients with severe, painful obstruction, placement of a ureteral double-J stent is the preferred method,[70,72,77] eventually associated with kidney drainage by percutaneous nephrostomy. Ureteral drainage allows time for hy-

dration and temporary urine acidification to dissolve calculi. In some patients, a complementary urological technique such as calculi extraction by ureteroscopy or, in exceptional circumstances, percutaneous nephrolithotomy may be advisable. ESWL is poorly effective because of the high content of proteins in the calculi, which makes them insensitive to fragmentation by shock waves. In most patients, conservative treatment is successful. In the large cohort evaluated by Herman et al.,[61] only 14% of affected patients required urological intervention. In our experience, among 126 patients with indinavir-containing calculi, only four required urological intervention, all in the form of ureteroscopy.

Prevention of renal complications of indinavir therapy is based on the above-mentioned pharmacokinetic characteristics of the drug. Theoretically, urine acidification should be the most effective therapy.[110] However, prolonged urine acidification to a pH urine <5.5 would be poorly tolerated and possibly harmful, especially in patients receiving concomitant treatment with sulfonamide derivatives. In addition, it may favour the development of uric acid nephrolithiasis as observed in one of our patients. However, short-term urine acidification in patients with symptomatic indinavir calculi or crystalluria may be effective to resolve the calculi episode and encourage spontaneous calculi passage.[101,111]

The safest, simplest and most effective prophylactic measure to prevent formation of indinavir-containing calculi is to add to the basal fluid intake of at least 1.5L fluid per day, to increase urine output during the 3 hours following each 800mg oral dose of indinavir. This may be achieved by ingestion of 150ml of fluids when taking the drug and every hour for 2 hours afterwards, as proposed in 1997.[91] Fluid intake may include lightly acidic beverages such as Coca-Cola® or similar products, which are acidified with phosphoric acid. Glycyrrhetinic acid (contained in liquorice) has been shown by Grases et al.[112] to markedly extend the precipitation time of indinavir, thus preventing deposition of indinavir crystals in renal tubules. However, this molecule may provoke hypokalaemia and hypertension as a result of inhibition of the 11β-OH steroid dehydrogenase, and such an approach should be used with caution.

Validity of recommendations to increase fluid intake when taking the drug was confirmed in our patients. The incidence of indinavir crystalluria decreased markedly in two-thirds of 44 patients followed over 1 year, and none of them had a recurrence of renal colic. In addition, we observed a significant reduction in the annual number of calculi from indinavir-treated patients referred to our laboratory after 1999, probably because of widespread information to physicians caring for HIV-infected patients.

Unfortunately, such advice is ineffective to prevent indinavir crystallisation in the gallbladder. We reported recently the case of an HIV-positive patient on long-term treatment with indinavir who developed cholelithiasis.[113] The gallbladder stone (10mm in diameter) was surgically removed and then analysed by infrared spectroscopy. Indinavir monohydrate was a major component of all layers of the gallstone and was present in the nucleus, in association with calcium bilirubinate and proteins. Before the cholecystitis episode, the patient had received indinavir 800mg three times daily over a 3-year period in association with several other drugs according to a triple therapy protocol (lamivudine and zidovudine, stavudine and didanosine).[113]

Today, therapeutic protocols for HIV are based on reduced doses of indinavir in association with ritonavir; such regimens increase the half-life of indinavir and are widely applied because of the good pharmacological results achieved with reduced adverse effects.[114]

4.2.2 Nelfinavir

Recently, nelfinavir, another protease inhibitor used in the treatment of HIV-positive patients, was reported by Engeler et al.[115] as a new cause of recurrent drug-induced calculi disease. The calculi composition was determined by liquid chromatography and mass spectrometry. It revealed 99% nelfinavir and 1% indinavir.

4.2.3 Other Antiviral Drugs

Although not yet described as part of urinary calculi, several antiviral drugs have been reported to

induce acute or chronic renal failure due to crystallisation in the kidney parenchyma.

Foscarnet has been observed in early segments of the nephron and within glomeruli of patients who developed renal insufficiency following repeated infusion of high doses (6–12 g/day) for cytomegalovirus infection.[116,117] The crystals were identified as calcium and/or sodium salts of foscarnet.[117] Similarly, several cases of acute renal failure induced by needle-shaped aciclovir crystals within renal tubules have also been reported, usually in association with high doses of the drug, especially when administered as an intravenous bolus, and low urine flow.[118-121] To date, no cases of foscarnet- or aciclovir-containing calculi have been reported.

As suggested by Fogazzi,[122] who pointed out the interest of examining urine sediment in various clinical conditions, the study of crystalluria is a useful tool to detect patients at risk of renal damage or for managing patients on treatment with drugs known for their ability to precipitate in urine.

4.3 Sulfonamides

First-generation sulfonamides were used for more than 60 years, and were shown early on to provoke drug-induced urolithiasis[1,2,123] or acute renal failure episodes caused by intratubular crystallisation of the drug.[2,124] Factors involved in the precipitation of sulfonamides in the urine are the high degree of urinary excretion, and the low solubility of the parent drug and its metabolites in urine, especially the N-acetyl metabolites, at usual urine pH. Favouring factors for the development of sulfonamide-containing calculi are a low urine output and a long-term treatment at high dose.[7,10] Although a number of cases were still observed up to the 1980s,[125] the development of sulfonamides with greater solubility and the availability of other antimicrobial agents have considerably reduced the incidence of renal complications of sulfonamides, with the exception of sulfadiazine.

Sulfadiazine is largely used for the treatment of toxoplasmic encephalitis in AIDS patients and transplant recipients on long-term immunosuppressive therapy, because sulfadiazine easily crosses the blood-brain barrier. In severe forms of cerebral toxoplasmosis, sulfadiazine is used at very high doses (4–8 g/day), which provoke heavy intratubular crystallisation of the poorly soluble metabolite N-acetylsulfadiazine, thus resulting in the rapid formation of bilateral calculi and/or acute renal failure secondary to tubular obstruction.[126-137] Over the last 25 years, we have observed 41 calculi composed of N-acetylsulfadiazine (figure 1), which was found in the nucleus in 93% of patients.[14] Among the 41 calculi, 39 were identified in the 1990s in AIDS patients. Unchanged sulfadiazine may also be present in calculi but infrequently constitutes the major component.

The main factors involved in sulfadiazine crystallisation are:

- high daily doses;
- quick liver N-acetylation of the drug;
- high urinary excretion of both unchanged drug and metabolites, especially N-acetyl derivatives, the solubility of which is low in respect to their urine concentration;
- low urine pH; and
- needle-shaped morphology of N-acetylsulfadiazine crystals, which may rapidly aggregate to form large agglomerates able to form calculi and obstruct renal tubules.

Low urine volume and urine stasis are additional worsening factors often involved in sulfonamide crystallisation. Multiple and/or bilateral nephrolithiasis associated with sulfasalazine therapy have been reported in a few patients with rheumatoid arthritis or ulcerative colitis.[138-141]

Sulfonamides still in use in other indications are much less lithogenic, in as much as their daily doses are much lower. Sulfamethoxazole, a component of the widely used cotrimoxazole (trimethoprim/sulfamethoxazole), is frequently associated with the crystalluria[142,143] in the form of N-acetylsulfamethoxazole hydrochloride losangic crystals (not to be mistaken for uric acid crystals), but this is rarely responsible for obstructive uropathy.[18,125,144] In 1994, Albala et al.[125] reported 40 observations of sulfonamide-containing urinary calculi. N-acetylsulfamethoxazole was the most frequent constituent

(33 cases), but N-acetylsulfadiazine (five cases) and N-acetylsulfisoxazole (two cases) were also found as calculi components. Only a few papers reporting N-acetylsulfamethoxazole-induced urolithiasis were published between 1972 and 1994,[125,145-148] thus confirming the low lithogenic potential of this compound, probably due to the losangic shape of the crystals (figure 3) which does not favour crystal retention within the kidney.

In 1969, Otto and Allesch[149] reported two cases of N-acetylsulfaperine-containing calculi. In 1986, one case of N-acetylsulfaguanidine nephrolithiasis was described by Réveillaud and Daudon;[11] five additional cases of asymptomatic N-acetylsulfaguanidine crystals were observed in non-acidic urine samples (urine pH between 6.6 and 7.4).[18]

4.3.1 Management and Preventative Measures

Curative and preventive treatment of sulfonamide-induced obstructive renal complications rely on the high solubility of the drug and its metabolites at alkaline urine pH. After the obstructive mechanism is diagnosed (e.g. the kidney echography shows dilation of the urinary tract and there is evidence heavy crystalluria when urine is examined), active alkalinisation of the urine by the intravenous or oral route is instituted and usually restores diuresis.[150] In patients with severe obstruction, urine derivation by ureteral stenting or, if not possible, by nephrostomy, may be indicated.

During sulfadiazine therapy, the mainstay of calculi prevention is alkaline hyperdiuresis during the whole duration of treatment, except in patients being simultaneously treated with indinavir. In these patients, a significant increase in fluid intake (>2 L/day) is needed to prevent the risk of crystallisation of either indinavir or sulfonamide.

4.4 Other Molecules

4.4.1 Silicate-Containing Drugs

Silica urolithiasis is frequent in grazing animals such as cattle and sheep, and in dogs.[151,152] Silicate calculi may develop in humans after long-term consumption of magnesium trisilicate as an antacid for oesophageal or gastric symptoms. Since the first cases reported by Hammarsten et al.[153,154] in Scandinavia in the early 1950s, about 30 cases have been reported worldwide, all observed in adults or teenagers.[155-164] Calculi were often entirely made up of amorphous silicon dioxide (silica).[157]

We observed nine cases of calculi in babies receiving colloid silica in their feeding bottle to thicken milk and thereby prevent oesophageal regurgitation.[165] ESWL was used in four cases and ureteroscopy in three cases. Opaline silica (figure 3) was found in the nucleus of all calculi, often surrounded by calcium oxalate and/or calcium phosphate. In several children, the calculi were not revealed until several years after silica withdrawal, underlining the importance of calculi analysis for understanding risk factors involved in calculi formation.

Silica calculi usually develop in patients receiving high daily doses of silicate-containing drugs, which are often ingested over a long period of time.[154-163] The most common form is magnesium trisilicate, which is present in a large number of antacid medications. In 1941, Page et al.[166] reported significantly increased silica levels in the plasma of individuals receiving oral pharmacological dosages of magnesium trisilicate. In correlation, silica excretion in urine also was increased. They suggested that a part of the magnesium trisilicate was converted into various silicic acids within the stomach, because of the very low gastric pH. According to their chemical form and hydration, orthosilicic and metasilicic acids may be partly absorbed in the gut and then silica excreted in urine. Analogous results were reported by Bailey[167] who investigated renal excretion of silica in cattle according to the diet.

Urine conditions that favour silica precipitation are debated. Silica-containing calculi are often found in animals,[168] the urine of which is more likely to be alkaline because of vegetable diet, and silica calculi from animals have been often shown to have components that are known to crystallise more readily in alkaline urine.[169,170] However, some *in vitro* animal studies have produced conflicting results, suggesting that acidic conditions favour precipitation of silica in urine.[171] It appears that the composition of the experimental medium is an im-

portant determinant of whether silicate precipitation occurs under *in vitro* conditions.[172] Indeed, silica urinary calculi often contain calcite or calcium phosphate, which crystallise in weakly acidic or alkaline urine.[172,173]

In our experience, metabolic investigation in five babies revealed that two predisposing conditions, that is neutral or alkaline urine pH (pH ≥6.6) and proteinuria, are needed to develop calculi containing amorphous silica. In three of the five patients, alkaline urine was associated with transient tubular acidosis. Hypercalciuria, which is often related to renal tubular acidosis, may explain the presence of both weddellite and carbapatite in the calculi. Proteinuria was also found in several patients and we observed peculiar gels composed of proteins admixed with silica in the form of very small grains (<1 micron) in the urine of the babies with silica calculi. As suggested by several authors,[172,174,175] the relationship between proteins and silica is very important, and could explain why the occurrence of silica calculi is very low with respect to the wide self-medication of silicate-containing drugs; the precipitation of silica in urine may be dependent on the urine protein content in addition to the pH value. In contrast with other calculi, silica-containing calculi have a high content of organic matrix (figure 3), which was estimated at about 12% by Forman et al. in calculi from beef cattle.[171] Other authors have emphasised the high protein content in human calculi.[154,156,159]

All calculi that contain amorphous silica are not related to silicate-containing drugs. Like herbivorous animals, humans who commonly eat vegetables and roots or ingest pica are exposed to a high intestinal load of silicates, a proportion of which is able to be absorbed by the gut.[176]

Of note, crystalline forms of silica such as α-quartz, which are found in association with other silicates or calcium carbonates and/or calcium sulfates, may be responsible for spurious calculi.[177,178] In some cases, silica-based mineral artefacts are collected either inadvertently or intentionally (possibly for psychiatric reasons) from the environment and submitted to analysis as true calculi by patients who complain of renal pain and/or calculi passage. This can result in erroneous medical diagnosis as observed in the literature.[179]

4.4.2 Amino-4-Quinoleines

During a period of about 20 years, glafenine (a potent analgesic used mainly in France and available since 1965) was responsible for several cases of nephrolithiasis and renal failure until its withdrawal in 1992.[11,180,181] Forty calculi from glafenine-treated patients were analysed at our laboratory (Laboratoire Cristal) [table IV]. Of note, several of these calculi did not become evident until more than four years after the drug was withdrawn. Calculi mainly consisted of free glafenic acid surrounding preformed calculi. The main urinary metabolite, glafenic acid glucuronide, is highly soluble. The chemical or enzymic deconjugation of the metabolite increases the urinary concentration of the poorly soluble free glafenic acid. In some patients, calculi were entirely composed of the drug admixed with large amounts of proteins.[182] Because of the high protein content, the radiolucent glafenic-induced calculi raised problems for radiological diagnosis.[183]

Calculi mainly affected female patients on long-term treatment with glafenine because of arthrosis who had concomitant urinary tract infection. This suggests possible involvement of bacteria in the lithogenic process, through either an increase in urine pH caused by urease-producing bacteria (*Proteus* spp.) or enzymic deconjugation of glafenic acid glucuronide caused by bacterial glucuronidase (*Escherichia coli*).

As reported for indinavir, glafenic acid calculi were also observed in the gallbladder of three patients,[184] bearing in mind that bile is another way for excretion of a number of drugs including poorly soluble ones that may occasionally crystallise. In two of the three patients, Enterobacteriaceae were isolated from bile cultures, suggesting, as in urine, the role of infection in calculi formation.

Other cases of amino-4-quinoleines-induced calculi have occasionally been reported.[185,186] Similarly to glafenine-induced calculi, all cases of antrafenine-induced urinary calculi were observed in patients who presented with concomitant urinary

tract infection, suggesting that bacteria were involved in the lithogenic process.[185] In contrast, the mechanism of crystallisation probably was not the same for floctafenine, which was identified as a glucuronide derivative in one case reported by Moesch et al.[186] and in two cases of our series.

4.4.3 Allopurinol

As an inhibitor of xanthine dehydrogenase, allopurinol is widely used for the treatment of hyperuricaemia. Allopurinol and its active (poorly soluble) metabolite, oxypurinol, are excreted via the urine.

Urinary calculi made up of either pure oxypurinol, as reported by Landgrebe et al.,[187] or of oxypurinol admixed with allopurinol were observed in patients receiving high doses (≥600 mg/day) of both allopurinol and oxypurinol for Lesh-Nyhan syndrome. More commonly, calculi composed of xanthine admixed with oxypurinol have been observed in children receiving normal to moderately high doses of allopurinol for Lesh-Nyhan syndrome.[188-194]

Apart from the Lesh-Nyhan syndrome, only two cases of oxypurinol-containing calculi have been reported, by Stote et al.[195] and by Potter and Silvidi.[196] The first case described a woman with regional enteritis with an ileostomy after removal of the colon and of a large portion of the ileum. Because of acidic urine and very low diuresis, she experienced recurrent uric acid lithiasis, which justified treatment with high-dose allopurinol (600–900 mg/day). While on allopurinol therapy, the patient experienced recurrent bilateral radiolucent calculi made of oxypurinol admixed with xanthine as a minor component.[195] In 1987, Potter and Silvidi[196] reported the case of a child presenting with episodes of acute renal failure related to acute phases of lymphoblastic leukaemia with high uric acid production. He was treated for 3 months with high doses of allopurinol. The patient died following a new episode of renal failure that was unresponsive to dialysis. Autopsy revealed obstructive uropathy, focal nephrocalcinosis, and multiple and bilateral kidney calculi, which were identified as a mixture of xanthine and oxypurinol with a low proportion of hypoxanthine.[196]

General measures for preventing allopurinol-induced calculi in patients at risk of developing xanthine and oxypurinol crystallisation in their urine rely on alkaline hyperdiuresis and adjustment of allopurinol dosage to the lowest effective dose.

4.4.4 Antibacterial Agents

Drug-induced nephrolithiasis has been reported in patients treated with quinolones such as flumequine,[197] oxolinic acid[198,199] or ciprofloxacin;[200] aminopenicillins such as amoxicillin[13] (figure 3) and ampicillin;[201] ceftriaxone (mostly in children)[14,202-205] and phenazopyridine.[11,206,207] Factors that favoured the development of nephrolithiasis were low urine output, high drug dosages and low urine pH (except for ciprofloxacin, which is less soluble in alkaline pH). In recent years, we identified two further cases of phenazopyridine calculi and seven calculi made of calcium ceftriaxonate, including a gallstone in an adult, which reminds us that gallstones are another possible complication of precipitating drugs, especially of ceftriaxone therapy.[205,208-211]

In contrast with first-generation quinolones,[18] fluoroquinolones produce crystalluria in alkaline urine.[212] Ciprofloxacin administered orally or intravenously to healthy volunteers caused crystalluria only at high doses and if urinary pH was alkaline.[213,214] Crystalluria was essentially asymptomatic and a unique case of obstructive ciprofloxacin urolithiasis was reported by Chopra et al.[200] However, some cases of toxic tubulointerstitial nephritis have been reported in patients while on pharmacological dosages of ciprofloxacin.[215-217] Ciprofloxacin and norfloxacin crystallise in urine as magnesium salts.[213,218,219] In our experience, these compounds were found in three urinary calculi (one case of norfloxacin and two cases of ciprofloxacin), but never in the nucleus, suggesting a low lithogenic power of these molecules (unpublished data). In agreement with this opinion, Swanson et al.[220] reported that norfloxacin crystals are occasionally observed but only in urine of patients receiving high doses of the drug, that is, 1200mg or more. Never-

theless, attention should be paid when using fluoroquinolones in patients with urinary tract infections caused by urease-producing bacteria and elevated urine pH.

Amoxicillin and ampicillin may crystallise in urine as the trihydrate form, which is sometimes responsible for reversible acute renal failure or gross haematuria.[221-224]

The risk for renal adverse effects with both quinolones and aminopenicillins is enhanced by the large needle-shape crystals of these compounds (figure 3), which may easily aggregate and be retained within the tubules. However, compared with the extensive use of these drugs, the crystallisation risk appears much lower than that of indinavir.

Nitrofurantoin was also involved in several cases of renal calculi and crystalluria.[225,226] A unique report of a nitrofurantoin-containing renal calculus was described in a 52-year-old patient who presented with a calculi blocked in an ureterocele. The calculus was made up of calcium oxalate covered by surrounding layers of nitrofurantoin, which had been prescribed for recurrent cystitis.[225]

4.4.5 Guaifenesin and Other Stimulants

Guaifenesin, a popular expectorant drug, was recently reported in the US as a cause of iatrogenic calculi following abusive consumption of this drug by self-medication as a stimulating product.[227,228] The calculi were made of the main metabolite of guaifenesin, the calcium salt of β-(2-methoxy-phenoxy)-lactic acid, which was identified as the main or exclusive compound of 30 calculi. The prevalence of this drug among 56 000 urinary calculi analysed during the collection period was 0.05%. Only one patient had a history of renal calculi. In the report by Assimos et al.,[228] seven calculi contained guaifenesin metabolites and one of them also contained some proportion of ephedrine.

Ephedrine was reported as the cause of an obstructive calculus in a young man who ingested 1–3g of ephedrine per day for 'stimulation'.[229] Popular stimulant preparations such as Ma-Huang extract, widely used in the US, have also been reported to induce calculi formation.[230] The calculi are made of ephedrine admixed with norephedrine and pseudoephedrine.

4.4.6 Miscellaneous

Two other drugs, primidone and methotrexate, have been described as a cause of renal failure because of massive crystallisation in renal tubules.[231-235] Because of the relatively low solubility of these drugs (primidone: 600 mg/L; methotrexate: 2 mmol/L at pH <5.5 and 10-fold greater at pH 7) and their high degree of urinary excretion, they were responsible for acute renal failure following overdose. As reported by Perazella,[20] 30–60% of patients treated with high-dose (intravenous) methotrexate are exposed to the crystallisation of the drug and risk of renal adverse effects, especially when urine is acidic. Because the drug is more soluble in alkaline urine, high urine flow and alkalinisation may prevent acute renal failure. No cases of drug-containing calculi have yet been reported.

5. Metabolically Induced Calculi

At variance with the above-mentioned cases of calculi made of the drug itself (section 4), iatrogenic calculi may result from the metabolic effects of the drugs. Depending on the type of metabolism in question, calculi induced by drugs may be radio-opaque calcium-containing, or radiolucent urate-containing calculi. The drugs involved in metabolically induced calculi and the composition of the corresponding calculi are summarised in table V and table VI.

5.1 Drug-Induced Calcium-Containing Radio-Opaque Renal Calculi

5.1.1 Calcium/Vitamin D Supplements

Calcium supplements, especially when associated with vitamin D, may result in hypercalciuria and nephrolithiasis, particularly in patients with underlying absorptive hypercalciuria.[236-238] Such a possibility should be kept in mind when treating postmenopausal women with calcium/vitamin D supplements.[239] To prevent nephrolithiasis, urinary calcium output should be determined before initiating such therapy and at regular intervals while the

Table V. Evolution over time of the overall proportion of drug-induced metabolic calculi, and distribution of the most frequently identified molecules, in an analysis of 37 621 urinary calculi over the period 1977–2002 (Laboratoire Cristal, Paris, France)

	Period I (1977–86)	Period II (1987–96)	Period III (1997–2002)
Total no. of stones analysed	4086	16 251	17 284
No. of drug-containing calculi[a]	59 (1.4)	112 (0.7)	70 (0.4)
Frequency of molecules identified (% of total drug-induced metabolic calculi for time period)			
Piridoxilate	27 (0.66)	15 (0.09)	0 (0)
Calcium + vitamin D supplements:	15 (0.37)	43 (0.26)	34 (0.20)
in renal failure	13 (0.32)	24 (0.15)	18 (0.10)
in other cases	2 (0.05)	19 (0.12)	16 (0.09)
Acetazolamide	1 (0.02)	19 (0.12)	10 (0.06)
Laxative molecules	6 (0.15)	11 (0.07)	3 (0.02)
Uricosuric drugs	4 (0.10)	4 (0.02)	7 (0.04)
Aluminium hydroxide	2 (0.05)	10 (0.06)	1 (0.006)
Corticosteroids	0 (0)	5 (0.03)	6 (0.03)
Naftidrofuryl oxalate	0 (0)	4 (0.02)	3 (0.02)
Others	1 (0.02)	1 (0.006)	3 (0.02)

a Total number of drug-induced metabolic calculi for the entire time period was 241 (0.6%).

patient is receiving treatment. Alternative treatments for prevention of osteoporosis should be proposed for the few patients who exhibit high urinary calcium excretion and increased calcium oxalate supersaturation while receiving calcium/vitamin D therapy. Alternatively, a thiazide diuretic can be given along with calcium/vitamin D supplementation.[238] Calcium and vitamin D supplementation as a cause of calcium-containing calculi is probably greatly underestimated because the calculi may become evident long after drug withdrawal.

A peculiar form of calcium oxalate calculi induced by vitamin D has been reported in patients with end-stage renal disease (ESRD) being treated with haemodialysis or peritoneal dialysis. Calculi were made of calcium oxalate monohydrate with a large proportion of proteins.[240-243] The likely mechanism is as follows: in ESRD patients with residual diuresis, the concentration of urinary oxalate and protein in the remaining functional nephrons is high. When the filtered calcium load is increased because of vitamin D supplementation given to counteract hypocalcaemia, the urinary calcium concentration (which is usually very low) may increase to over 1 mmol/L. This leads to calcium oxalate supersaturation and the crystallisation of predominantly whewellite, if the oxalate concentration is in excess of 0.5 mmol/L, admixed with proteins.[243]

5.1.2 Carbonic Anhydrase Inhibitors

Acetazolamide is widely used in the treatment of glaucoma[244] and also as an anticonvulsant in the treatment of epilepsy.[245,246] As a carbonic anhydrase inhibitor, acetazolamide acts on the proximal renal tubule, blocking the reabsorption of bicarbonate in parallel with inhibiting the excretion of hydrogen ions. This action results in intracellular acidosis, which enhances tubular reabsorption of citrate ions, thus resulting in hypocitraturia. Carbonic anhydrase inhibitors, such as acetazolamide[247-254] and its analogues methazolamide,[255] dorzolamide[256] and diclofenamide (dichlorphenamide),[257] are responsible for the frequent development of nephrolithiasis. This was first reported by Persky et al.[247] in 1956, and the estimated incidence is nearly 10% of treated patients.[244,258] Nephrocalcinosis has also been reported.[257,259,260]

As determined by Ahlstrand and Tiselius[261] a combination of marked hypocitraturia and elevated urine pH is a lithogenic factor in patients treated with acetazolamide. Such urine composition favours the precipitation of calcium phosphate.[262] Carbapatite was the predominant constituent of 30 calculi examined at our laboratory from patients being treated with carbonic anhydrase inhibitors (table V). A history of urolithiasis, or underlying hypercalciuria, are favouring factors for development of uroli-

Table VI. Metabolic drug-induced calculi: usual stone composition

Drug or drug family	Crystalline form in urine and/or calculi
Radio-opaque calculi	
Calcium/vitamin D supplements:	
in patients with normal renal function	Mixed calcium oxalates and calcium phosphates
in patients with end-stage renal failure	Whewellite admixed with proteins
Carbonic anhydrase inhibitors: acetazolamide; methazolamide; zonisamide; dorzolamide; diclofenamide; dichlorphenamide; topiramate	Calcium phosphates, mainly carbapatite, with or without calcium oxalates
Piridoxilate	Whewellite and calcium oxalate trihydrate
Furosemide	Calcium oxalate or mixtures of calcium oxalate and calcium phosphates
Magnesium trisilicate-aluminium hydroxide	Magnesium ammonium phosphate
Carbonate- or bicarbonate-containing drugs	Calcite admixed with calcium phosphates
Corticosteroids	Mixed calcium oxalates and calcium phosphates
Ascorbic acid (vitamin C)	Calcium oxalates
Naftidrofuryl oxalate	Calcium oxalates, mainly whewellite
Nimesulide	Calcium oxalates
Antibacterials	Calcium oxalates
Alkalinising drugs	Calcium phosphates
Radiolucent calculi	
Aluminium hydroxide	Aluminium magnesium potassium urate complex
Laxative drugs	Ammonium urate ± uric acid ± calcium oxalates
Uricosuric drugs	Uric acids
Allopurinol (see table I)	Xanthine (+ oxypurinol)
Alkalinising drugs: sodium or potassium bicarbonate, other carbonate salts	Sodium urate, sodium potassium urate, potassium urate, ammonium urate
Acidifying drugs: ammonium chloride, phosphoric acid, etc.	Uric acid

thiasis in these patients. Treatment of this complication is difficult if treatment with the drug has to be maintained for an imperative ophthalmological indication. Fortunately, locally administered forms of these drugs are now available and will reduce the incidence of this complication.

Of note, newer anticonvulsant drugs such as topiramate[263-265] and zonisamide[264,266] possess carbonic anhydrase inhibitory properties and consequently may induce calcium phosphate calculi.[264,267-269]

5.1.3 Piridoxilate

Piridoxilate, an equimolar combination of glyoxylate and pyridoxine (vitamin B6), was largely used in France and in some European countries in the 1970s and 1980s as an arterial vasodilator for the treatment of coronary and peripheral artery disease. More than 100 cases of nephrolithiasis were reported[270] in patients on long-term treatment with piridoxilate. Whewellite was the major component of calculi, and urine contained crystals of calcium oxalate trihydrate, normally a very infrequent component in human urine, which was responsible for a peculiar morphology of the calculi.[23,271] Hyperoxaluria was found in all patients[23,272] and in some cases was associated with nephrocalcinosis[273] and severe renal failure.[274,275] This very active and recurrent form of iatrogenic nephrolithiasis has disappeared since the withdrawal of piridoxilate in 1992.

5.1.4 Furosemide

Contrary to thiazide diuretics, which decrease urinary calcium excretion, furosemide induces calciuria. Several cases of furosemide-induced nephrolithiasis and nephrocalcinosis have been reported in premature neonates receiving long-term furosemide therapy for patent ductus arteriosus and later for

chronic lung disease.[276-283] Furosemide-treated infants with renal calcification had calcium excretion up to 20 times higher than age-matched premature infants not treated with furosemide. When a thiazide diuretic was given in addition to furosemide, a 4- to 15-fold decrease in calcium excretion was observed and dissolution of renal calcifications was documented.[276,284] Calculi composition revealed calcium oxalate[278] or, more often, a mixture of calcium oxalate and calcium phosphate.[276] In some patients, nephrolithiasis was associated with cholelithiasis.[277] Nephrocalcinosis may also develop in older, full-term infants treated with long-term furosemide for congestive heart failure.[285-287]

In spite of its widespread use, no case of furosemide-associated urolithiasis has been reported in adults. However, recently, medullary nephrocalcinosis was reported in 18 young women who abusively took long-term, high-dose furosemide (>100 mg/day) for slimming.[288]

Excessive calcium excretion is probably not the only mechanism for nephrolithiasis and nephrocalcinosis induced by furosemide therapy. Chronic hypokalaemic metabolic alkalosis and chloride deficiency with high urine pH is a frequent finding; this resembles the metabolic conditions of Bartter's syndrome,[289] which itself may be associated with calcium-containing calculi.

5.1.5 Antibacterials

Long-term or frequent treatment with antibacterials may alter gut microbial composition and, in particular, may destroy the gut commensal *Oxalobacter formigenes*. Such microorganisms normally degrade oxalate ions in the gut lumen. In the absence of *O. formigenes*, an increased proportion of oxalate ions is absorbed and then excreted in urine, thus resulting in increased oxaluria and calcium oxalate supersaturation. This mechanism could explain the frequent occurrence of calcium oxalate nephrolithiasis in patients with cystic fibrosis.[290] Such a mechanism was also suggested as a possible factor for calcium oxalate nephrolithiasis in individuals who formed idiopathic calcium calculi.[291]

Destruction by antibacterials of other microorganisms such as *Enterococcus faecalis* or lactic acid bacteria, which similarly degrade oxalate, may also contribute to increased oxaluria.[292,293] Conversely, as suggested by the authors, supplementation with *O. formigenes* or lactic acid bacteria could be of interest to reduce oxaluria and the risk of calculi formation.[291,293]

5.1.6 Alkalinising Drugs

Excessive alkalinisation by bicarbonate salts may induce massive calcium phosphate crystallisation and calculi formation, for instance, in cystinuric patients with insufficient diuresis. Not uncommonly, calcium phosphate deposits are found within cystine calculi or surrounding cystine calculi removed from patients whose urine was alkalinised in order to increase cystine solubility. More rarely, calcium phosphate calculi containing only pure calcium phosphate in the nucleus and a low proportion of cystine within the calculi are observed as the result of excessive urinary alkalinisation, as we observed in one patient.

5.1.7 Other Drugs

Less frequently, other drugs have been reported to induce metabolic calcium nephrolithiasis.

Antacid drugs are involved in nephrolithiasis in three different ways depending on the drug composition. First, silica calculi can result from long-term magnesium trisilicate consumption, as mentioned above (see section 4.4.1). Secondly, sodium bicarbonate or other carbonate salts (often associated with high consumption of milk) can induce nephrolithiasis. The products were widely used as antacid preparations, often by self-medication, before the era of gastric proton-pump inhibitors. Several cases of recurrent nephrolithiasis developing in patients who ingested excessive amounts of such products have been reported.[11,294,295] In our experience, calculi composition associated with these types of antacids was a mixture of calcite (calcium carbonate anhydrous) and carbonated calcium phosphate.[11] The third group of antacid drugs includes aluminium salts that are able to complex phosphate in the intestinal lumen, thus inducing hypophosphataemia, osteomalacia and secondary hyperparathyroidism,[296-298] which occasionally may be complicated by radio-opaque nephrolithiasis.[299] In 1981,

Millette and Snodgrass[300] reported the case of a man who ingested large amounts of magnesium trisilicate-aluminium hydroxide preparation. He developed acute renal failure and multiple renal calculi that were surgically removed. Calculi analysis revealed they were composed of magnesium ammonium phosphate related to high urine pH and high magnesium concentrations found in both the serum and urine of the patient. [300]

Corticosteroid therapy induces hypercalciuria and osteopenia. However, formation of urinary calculi appears to be very infrequent,[301,302] but it is perhaps underestimated. Dexamethasone, used in severely premature infants with bronchopulmonary dysplasia, may induce hypercalciuria and renal calcifications.[303]

Antiepileptic drugs such phenytoin, used in the long-term, are known to induce excess hepatic vitamin D degradation and secondary hyperparathyroidism, resulting in osteomalacia and, sometimes, nephrolithiasis.[304]

Ascorbic acid (vitamin C) overdosing has been reported as a risk factor for calcium oxalate nephrolithiasis. A dose of 1000 mg/day augments oxalate excretion by 6–13 mg/day,[305] and may induce calcium oxalate calculi.[306] Recently, Auer et al.[307] reported the case of a patient who developed haematuria associated with large aggregates of calcium oxalate dihydrate crystals following ingestion of large doses of vitamin C. Comparing the effect of an oral dose of ascorbic acid 2 g/day in healthy individuals and patients who form calcium oxalate stones, Traxer et al.[308] found that oxaluria increased in both groups but urine oxalate increase was significantly higher in stone formers. The authors recommend limiting ascorbic acid intake to <2 g/day in patients who form calcium oxalate stones. As observed by Chalmers et al.,[309] ascorbate supplementation may induce oxalate synthesis in the gut to a greater extent in patients who form calcium calculi than in those who do not; this would result in an increased amount of oxalate absorbed by the intestine and consequently higher urinary excretion of oxalate. However, at the epidemiological level, Curhan et al.,[310,311] who investigated the risk of developing calcium calculi related to the daily ascorbic acid intake, failed to observe a positive relationship between high ascorbic acid ingestion and the risk of forming calcium calculi. These findings suggest that only predisposed individuals are particularly sensitive to ascorbic acid load, which must be kept in mind among possible risk factors for nephrolithiasis in patients who form calculi.

Naftidrofuryl oxalate, used as a vasodilator by intravenous infusion, may induce hyperoxalaemia and hyperoxaluria with calcium oxalate crystal deposits in renal tubules, thus inducing renal failure.[312] Long-term oral therapy with naftidrofuryl oxalate has been shown to favour hyperoxaluria and calcium oxalate crystalluria in elderly patients[313] and may contribute to calcium oxalate calculi formation, especially in patients with low diuresis.[314]

Nimesulide, a new-generation NSAID which selectively inhibits cyclo-oxygenase 2 (COX-2) has been recently reported to provoke an acute reversible renal failure with multiple calcium oxalate crystals in tubular cells at renal biopsy.[315] This observation suggests a nephrotoxic effect of nimesulide, but the origin of the numerous calcium oxalate crystals observed on biopsy is unclear.

Acute deposition of calcium oxalate crystals in the kidneys may also result from xylitol infusions, which produce endogenous oxalate by oxidisation of the carbohydrates.[316-320]

5.2 Drug-Induced, Purine-Containing, Radiolucent Renal Calculi

5.2.1 Aluminium-Containing Drugs

Aluminium-magnesium hydroxide was largely used as a gastrointestinal antacid drug. Long-term, high-dose use may induce hypophosphataemia, hypercalciuria and osteopenia, but nephrolithiasis appears to be an infrequent complication (see section 5.1.7). Aluminium hydroxide was also long used as a phosphate binder for the treatment of hyperphosphataemia in uraemic patients, until the severe encephalic complications of aluminium intoxication became known. To date, we have observed 13 cases of nephrolithiasis associated with aluminium hydroxide (table V); these occurred in pa-

tients on maintenance haemodialysis who were treated with aluminium hydroxide 3–10 g/day.[243] Calculi were made of complex aluminium, magnesium and potassium urate admixed with proteins, and sometimes with calcium oxalate.

5.2.2 Laxative Drugs

Laxative abuse, usually resulting from self-medication in anorexic women, may provoke the formation of radiolucent calculi made of ammonium urate.[13,321,322] The mechanism is as follows. Chronic diarrhoea induced by laxatives results in the loss of bicarbonate, sodium, potassium, phosphate and magnesium. Animal protein and dairy product intake is often low, thus contributing to low phosphate urine excretion. Consequently, acid load elimination is almost entirely through increased ammoniagenesis. High urine ammonia concentration, in the face of high urate concentration, leads to ammonium urate calculi when urine pH is ≥6.0. Such composition of calculi in a thin woman should alert to the possibility of laxative abuse (often associated with diuretic abuse).

5.2.3 Uricosuric Drugs

Uricosuric drugs such as benziodarone, benzbromarone or tienilic acid (ticrynafen) are used to reduce hyperuricaemia by increasing urinary uric acid excretion. Therefore, they entail the risk of uric acid nephrolithiasis especially in patients with a history of gout or hyperuricosuria.[11,323-325] Other drugs with uricosuric properties may also induce uric acid nephrolithiasis and/or acute renal failure because of massive urate deposition in the kidneys.[326-330] In patients with gout, inhibition of uric acid production by allopurinol or other xanthine dehydrogenase inhibitors should be a preferred mode of therapy. In patients with hyperuricaemia who are intolerant of allopurinol,[330] uricosuric drugs should be used in association with increased diuresis and, if necessary, strategies for alkalinising urine.

5.2.4 Allopurinol

Allopurinol may induce xanthine calculi in patients with the Lesh-Nyhan syndrome, which is characterised by heavy hyperuricaemia and hyperuricosuria and abolished feed-back control,[188] when treated with high doses of allopurinol. Prevention is difficult, but strategies should be based on use of the lowest effective dose of allopurinol and alkaline hyperdiuresis.

5.2.5 Urine pH Modifiers

Urinary acidification by means of ammonium chloride or phosphoric acid may provoke the formation of uric acid calculi when urine pH is consistently maintained below 5.2.[14]

Conversely, alkalinising treatments prescribed in order to dissolve radiolucent uric acid calculi sometimes results in the deposition of insoluble urate salts, either sodium urate monohydrate, sodium potassium urate, ammonium urate or calcium urate hexahydrate. Urate deposition may be a consequence of low diuresis and a high concentration of sodium and/or potassium or other cations in patients in whom uric acid calculi form because of hyperuricosuria rather than permanently acidic urine. Increasing diuresis and reducing dietary salt intake are helpful measures to prevent such adverse effects of alkalinising therapy.

6. Conclusion

In conclusion, drug-induced calculi, although they represent only 1–2% of renal calculi, deserve consideration because most of them are preventable.

Triamterene was the leading cause of drug-containing renal calculi in the 1970s and, despite repeat recommendations about its use, it is still currently responsible for a significant number of calculi. In the past decade, drugs used for the treatment of HIV-positive and AIDS patients, namely indinavir and sulfadiazine, have become the most frequent cause of drug-containing calculi. Beside these drugs, a number of other molecules that are poorly soluble and are largely excreted in the urine may induce nephrolithiasis.

Infrared spectrophotometry is one of the most efficient methods for the diagnosis of drug-containing calculi or urine crystals, because of their specific spectra. However, by themselves, analytical methods are unable to identify urinary calculi induced by the metabolic effects of drugs, the diagnosis of

which relies on careful clinical inquiry. Therefore, the incidence of such calculi, especially those resulting from calcium/vitamin D supplementation, is probably underestimated.

Development of drug-induced renal calculi most often complicates high-dose, long-duration drug treatments, but there also exist specific patient risk factors in relation to urine pH, urine output and other parameters, which provide a basis for preventive or curative treatment of calculi.

Better awareness of the possible occurrence of lithogenic complications, and close surveillance of patients on long-term drug therapy with lithogenic potential, especially those with a history of urolithiasis, should reduce the incidence of drug-induced nephrolithiasis. In addition, recent advances in understanding of the pathogenesis and pathophysiology of drug-induced renal calculi will help in implementing the most appropriate prophylactic and therapeutic measures.

Acknowledgements

No sources of funding were used to assist in the preparation of this manuscript. The authors have no conflicts of interest that are directly relevant to the content of this manuscript.

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