Drug-Induced Urinary Calculi

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Urinary calculi may be induced by a number of medications used to treat a variety of conditions. These medications may lead to metabolic abnormalities that facilitate the formation of stones. Drugs that induce metabolic calculi include loop diuretics; carbonic anhydrase inhibitors; and laxatives, when abused. Correcting the metabolic abnormality may eliminate or dramatically attenuate stone activity. Urinary calculi can also be induced by medications when the drugs crystallize and become the primary component of the stones. In this case, urinary supersaturation of the agent may promote formation of the calculi. Drugs that induce calculi via this process include magnesium trisilicate; ciprofloxacin; sulfa medications; triamterene; indinavir; and ephedrine, alone or in combination with guaifenesin. When this situation occurs, discontinuation of the medication is usually necessary.

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Albeit a rare occurrence, certain medications used to treat a diverse range of disease processes can induce urinary stone disease. Medication-induced calculi can be composed of the drug or one of its metabolites, and their formation may be promoted by the urinary supersaturation of these substances. Alternatively, the drug may induce physiologic changes that facilitate the formation of "metabolic stones." Composition and radiographic imaging characteristics of drug-induced calculi are listed in Table 1.

Table 1
Plain Radiographic Imaging Characteristics of Drug-Induced Calculi

Drug	Primary Stone Composition	Status on Plain Radiography
Loop diuretics	Calcium oxalate	Radiopaque
Acetazolamide	Calcium phosphate	Radiopaque
Topiramate	Calcium phosphate	Radiopaque
Zonisamide	Calcium phosphate	Radiopaque
Laxatives (when abused)	Ammonium acid urate	Radiolucent
Magnesium trisilicate	Silica	Poorly radiopaque
Ciprofloxacin	Ciprofloxacin	Radiolucent
Sulfa medications	Sulfa	Radiolucent
Triamterene	Triamterene	Poorly radiopaque
Indinavir	Indinavir	Radiolucent
Guaifenesin/ephedrine	Guaifenesin/ephedrine	Radiolucent

Drug-Induced Metabolic Calculi

Loop Diuretics

Loop diuretics, such as bumetanide and furosemide, inhibit both sodium and calcium resorption in the thick ascending limb of the loop of Henle. In addition to exerting a diuretic effect, this mechanism of action produces a hypercalciuric state. Renal calculi have been noted in up to 64% of low-birth-weight infants receiving furosemide therapy.[1] Furthermore, the hypercalciuric effect of furosemide in infants is enhanced by a reduced glomerular filtration rate and immature hepatic function, which contribute to significantly prolonging the half-life of this drug.[2] The calculi isolated from these patients are composed exclusively of calcium oxalate.[3]

Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors, such as acetazolamide, act in the proximal tubule where they block resorption of sodium bicarbonate. Consequently, prolonged use of carbonic anhydrase inhibitors may lead to a hyperchloremic metabolic acidosis, in which urinary pH is increased and urinary citrate is decreased. Acetazolamide may be used by patients with glaucoma, as it reduces the flow of the aqueous humor, and by mountain climbers, as the bicarbonate diuresis and resultant metabolic acidosis increase ventilation and arterial oxygenation. Acetazolamide has historically been used to treat epilepsy but is employed for this purpose less commonly in recent times, as more effective medications have been developed. Patients who take acetazolamide on a long-term basis are at increased risk for the development of calcium phosphate calculi due to the metabolic alterations mentioned above.[4,5]

Topiramate is an effective and prevalent anti-epileptic medication used in patients who have partial or refractory seizures. Topiramate acts on neuronal transmission by modulating voltage-gated sodium ion channels, potentiating γ-aminobutyric acid (GABA) inhibition, blocking excitatory glutamate neurotransmission, modulating voltage-gated calcium ion channels, and inhibiting certain isoenzymes of carbonic anhydrase (CA-II and CA-IV). The precise mechanism by which topiramate exerts its antiseizure effect is not known.[6]

Wilner and colleagues[7] found that 1.5% of patients exposed to topiramate reported the occurrence of urinary calculi. One explanation for this occurrence may be that topiramate inhibits CA-II and CA-IV. Kuo and colleagues[8] reported 2 cases of topiramate-induced calculi. It should be noted that these authors described calcium phosphate calculi, supporting their hypothesis that topiramate induces a metabolic acidosis, with resultant hypocitraturia and alkaline urine. Preventive measures include high fluid intake, limited sodium intake, and consumption of citrate-containing fluids. Furthermore, patients receiving long-term topiramate therapy may require bone densitometry testing to detect early calcium loss secondary to acid buffering by bone.

Zonisamide is a sulfonamide agent that exerts an anti-epileptic effect through blockade of T-type calcium channels and GABA potentiation. Zonisamide also has weak carbonic anhydrase activity.[9] Initial trials of this medication found a 4% incidence of renal calculi. Kubota and colleagues[10] reported a series of patients who developed alkaline urine, hypercalciuria, and calcium phosphate calculi while receiving this medication. In all patients, the urinary calculi resolved with cessation of zonisamide and supportive therapy.

Laxatives

Ammonium acid urate calculi are more frequent among patients with persistent diarrhea and have been particularly associated with laxative abuse. In order for these calculi to form, urine must be supersaturated with both ammonia and uric acid. Ammonia is excreted by the proximal tubule as a means to eliminate

nonvolatile acid. Excess ammonia-ion formation can be seen with starvation, dehydration, or consumption of acid-forming foods or toxins. Uric acid solubility is dependent on urine pH: At a pH below the pKa of uric acid, all of the solute will be in the form of undissociated acid. As the pH rises, an increasing proportion will be in the monohydrogen form. In most urine, this form will be found as the sodium salt, but it may also combine with ammonium if an excess of this ion is present. Patients with chronic diarrhea often have low urine volumes and acidic pH. Studies of patients who form ammonium acid urate stones have demonstrated a pattern of mineral excretion that produces marked supersaturation with respect to ammonium urate.

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Ammonium acid urate calculi are radiolucent unless mixed with calcium. Although they may be mistaken for pure uric acid stones, they do not readily dissolve with urinary alkalinization. Dick and colleagues[11] found that discontinuation of laxatives may lead to correction of the urinary abnormalities. In 1 patient in their series, a 12-mm stone disappeared following 18 months of increased fluid intake and cessation of laxatives. Laxative abuse should be suspected in patients who form ammonium acid urate stones in the absence of bowel disease or urinary tract infection.

Calculi due to Urinary Supersaturation of a Drug or Its Metabolite

Magnesium Trisilicate

Silica is a ubiquitously distributed element that is consumed regularly in foods such as vegetables, whole grains, seafood, and even drinking water. Magnesium trisilicate is a medication that is available without a prescription for the treatment of symptoms of gastroesophageal reflux disease. Although dietary silicate is easily excreted in the urine, the consumption of excessive amounts of magnesium trisilicate can induce silicate stone formation. Farrer and Rajfer[12] reported the occurrence of a silicate renal calculus in a habitual abuser of magnesium trisilicate antacids. Silicate calculi are poorly radiopaque and easily treated with conventional lithotripsy methods. Prevention of recurrence can be assured if the patient eliminates the use of magnesium trisilicate antacids.

Ciprofloxacin

Ciprofloxacin is a fluoroquinolone antibiotic used to treat complicated and uncomplicated infections. It is nearly insoluble at neutral or alkaline pH and crystallizes in excreted alkaline urine of animal models. In humans, ciprofloxacin crystalluria may be induced when urinary pH is greater than 7.3 and doses greater than 1000 mg are administered.[13] Chopra and colleagues[14] reported a patient with bilateral ureteral obstruction due to calculi composed largely of ciprofloxacin. Ciprofloxacin calculi are radiolucent on plain radiography and may be best delineated by contrast pyelography.

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Sulfa Medications

The administration of sulfonamides can be complicated by the development of crystalline aggregates of these drugs.[15] Sulfamethoxazole-trimethoprim is a commonly employed antibiotic. Siegel[16] reported a case of an obstructing ureteral calculus composed of a pure metabolite of the sulfamethoxazole-trimethoprim combination. Of the sulfonamides, sulfadiazine, a medication commonly used to treat acquired immunodeficiency syndrome and toxoplasmic encephalitis, has particularly low urine solubility. Sasson and colleagues[17] and Colebunders and colleagues[18] reported cases of sulfadiazine-induced obstructive nephropathy in patients receiving the drug for cerebral toxoplasmosis. The solubility of sulfonamides is greatly enhanced by increased urinary pH, and sulfonamide-induced calculi may be avoided with adequate hydration and urinary pH manipulation. Sulfa-induced calculi are radiolucent on plain radiography.

Triamterene

Triamterene is a potassium-sparing diuretic that exerts its effects by inhibiting the resorption of sodium ions in exchange for potassium and hydrogen ions at the distal tubule. Triamterene is often used to treat edema as well as hypertension. The exact mechanism by which this drug promotes urinary calculus formation is unclear, although it is hypothesized that precipitation of triamterene and its metabolites provides a scaffold for nucleation and subsequent calculus growth.

Carr and colleagues[19] report that

21% of triamterene stones are pure triamterene, with the remainder being mixed stones.[19] Triamterene calculi cannot be dissolved by pH manipulation and, rather, must be treated with conventional lithotripsy techniques. The formation of triamterene calculi can be avoided by eliminating use of the medication. Triamterene is faintly radiopaque on plain radiography, although it does not have the density of stones such as calcium oxalate.

Indinavir

A frequently encountered drug-induced stone is that composed of the protease inhibitor indinavir, a medication that is commonly used to treat human immunodeficiency virus infection. A significant number of patients who receive this drug develop symptoms and signs of indinavir nephrolithiasis.[20] Pure indinavir stones are not detectable with standard radiography or computerized tomography. Some patients form stones that contain a calcium component, which may be radiographically visible, as well as the drug.[21] Hydration and analgesic therapy are recommended for initial treatment of indinavir stones. Indinavir therapy may need to be temporarily or permanently discontinued, in which case another protease inhibitor may be prescribed. Invasive intervention may be necessary for patients with prolonged renal obstruction, signs of sepsis, or unremitting symptoms.

Guaifenesin and Ephedrine

Preparations containing guaifenesin and ephedrine are available in the United States on an over-the-counter basis. Ephedrine, which may be derived from certain types of evergreen plants of the genus *Ephedra*, is an easily attainable drug that is purported to promote euphoria, increase energy, heighten sexual sensation, increase muscle mass, and effect weight loss. Blau[22] has described the development of ephedrine calculi in patients who chronically abuse this medication.

Triamterene calculi cannot be dissolved by pH manipulation and, rather, must be treated with conventional lithotripsy techniques.

A nonprescription combination of ephedrine and guaifenesin is manufactured for its bronchodilation and expectorant properties. Assimos and colleagues[23] report calculi containing both guaifenesin and ephedrine in persons consuming large quantities of over-the-counter preparations containing these substances. These calculi should be treated similarly to other types of calculi. Substance abuse counseling is recommended after calculi treatment to help limit stone recurrence. These calculi are radiolucent on plain radiographic imaging.

Conclusion

Stone disease may be caused by drugs used to treat a number of disease processes. A stone event may be a manifestation of a drug-induced metabolic abnormality, and correction of the disorder may eradicate or dramatically attenuate stone activity. Alternatively, the drug or its metabolites may crystallize and be the primary constituent of the calculus. When this situation occurs, the drug usually needs to be discontinued and alternative therapy instituted. ■

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Main Points

- Urinary calculi can be induced by a number of medications used to treat a variety of conditions.
- Loop diuretics, carbonic anhydrase inhibitors, and abused laxatives can cause metabolic abnormalities that facilitate the formation of stones. Correction of the metabolic abnormality can eliminate or greatly attenuate stone activity.
- Magnesium trisilicate; ciprofloxacin; sulfa medications; triamterene; ephedrine, alone or in combination with guaifenesin; and indinavir may induce calculi via urinary supersaturation. Eliminating such calculi usually involves discontinuation of the medication and initiation of an alternative therapy.

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