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CASE REPORT

Acute Kidney Injury in Patients with Inactive Cytochrome P450 Polymorphisms

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Medications are a major source of acute kidney injury, especially in critically ill patients. Medication-induced renal injury can occur through a number of mechanisms. We present two cases of acute kidney injury (AKI) where inactive cytochrome P450 (CYP) polymorphism may have played a role. The first patient developed a biopsy-proven allergic interstitial nephritis following urethrotomy. Genetic testing revealed the patient to be heterozygous for an inactivating polymorphism CYP2C9*3 and homozygous for an inactivating polymorphism CYP2D6*4. Patient had received several doses of promethazine, which is metabolized by CYP2D6*4. Another patient developed AKI on several occasions after exposure to lansoprazole and allopurinol. CYP testing revealed the patient to be homozygous for inactivating polymorphism CYP2C19*2, which is responsible for the metabolism of lansoprazole. These are the first two cases of AKI associated with non-functional polymorphisms of cytochrome P450 superfamily. While the exact mechanism has not been worked out, it introduced the possibility of a new source of kidney injury.

Keywords acute kidney injury, cytochrome P450, interstitial nephritis

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INTRODUCTION

Nephrotoxic drugs are a contributing factor to acute kidney injury (AKI) in 19–25% of critically ill patients.[1,2] A number of mechanisms have been identified.[3] Drugs that inhibit angiotensin-converting enzyme can injure the kidney by their hemodynamic effects. Others such as aminoglycosides or platinum-based medications cause direct cellular toxicity, resulting in acute tubular necrosis. Tubular injury can also be the result of osmotic cellular damage (iodinated contrast and mannitol) or precipitation/crystallization-causing obstruction (indinavir and methotrexate). Glomerular injury has been reported with gold. Finally, immune-mediated interstitial damage in the form of acute interstitial nephritis (AIN) is commonly seen with antibiotics. In some cases, drugs like non-steroidal anti-inflammatory drugs (NSAIDs) can injure the kidney by more than one mechanism.

AIN is an important cause of AKI and is found in 2–3% of all renal biopsies.[4,5] This number is likely to be underrepresentive of the true incidence, as most cases are not biopsied. Unfortunately, renal biopsy is the only definitive way of diagnosing AIN, which should show interstitial edema and a cellular infiltrate of T lymphocytes and monocytes.[6] AIN has four main etiologies: drugs, infections, immune-mediated diseases, and idiopathy.[7,8] The most common cause is a drug hypersensitivity reaction.[6,7] Drugs most commonly implicated in AIN include penicillins, cephalosporins, non-steroidal anti-inflammatory drugs, proton pump inhibitors, and histamine H2-receptors blockers. We report two cases of AKI in patients with

inactive polymorphisms of cytochrome P450, which we hypothesize may have played a role in inducing the renal injury.

CASE REPORT

Patient 1

A 58-year-old male with a history of recurrent urothelial carcinoma of the bladder underwent urethrotomy for ureteral stricture. His only daily medication was a multivitamin. His allergies were to azithromycin and ofloxacin, both of which gave him a headache. Perioperatively he received prophylaxis with ciprofloxacin (500 mg × 2), ampicillin (2 g), and gentamicin (80 mg), while a single dose of ketorolac (60 mg) and three doses of promethazine (12.5 mg) were given postoperatively for pain and nausea. The procedure was complicated by urethral bleeding, and the patient was admitted for observation. The next day his serum creatinine (Scr) was noted to be 4.4 mg/dL. Patient had no labs prior to surgery and his only Scr on record was 1.0 mg/dL, measured eight years earlier. The Scr continued to rise until it reached 11.3 mg/dL four days later. He had no uremic symptoms at that time. A renal ultrasound was negative for hydronephrosis and revealed slightly elevated resistive indices in both kidneys. Urinalysis showed eosinophiluria without significant proteinuria and a fractional excretion of sodium greater than 1%. The urine culture was negative. A renal biopsy was performed, revealing an acute allergic interstitial nephritis. Minimal chronic sclerosis changes accompanied diffuse infiltrates of eosinophilic and mononuclear cells. Prednisone (60 mg/d) was started and maintained for 5–6 weeks, and the patient had a complete recovery (Scr = 1.3 mg/dL) of renal function without ever requiring dialysis. Genetic testing showed the patient to be heterozygous for an inactivating polymorphism CYP2C9*3 and homozygous for an inactivating polymorphism CYP2D6*4, the cytochrome which metabolizes promethazine.

Patient 2

A 50-year-old male underwent autologous stem cell transplantation (SCT) for immunoglobulin light chain amyloidosis. He was on no medication prior to his SCT and reported no medical allergies. He was conditioned with melphalan (200 mg/m^2). Posttransplant course was complicated by severe mucositis with nausea, vomiting, and odynophagia. This eventually required management with a feeding tube. At that time, his Scr increased to 3.2 mg/dL (baseline = 1.4 mg/dL) but improved with hydration. At one month, Scr was 2.1 mg/dL but increased to 2.9 mg/dL four weeks later. Lansoprazole, which was started six weeks earlier, was discontinued. Despite this, Scr rose to 3.8 mg/dL. Penicillin (prophylaxis after SCT) was stopped, and prednisone (60 mg/day) was started. Scr returned to 2.1 mg/dL and prednisone was tapered over six weeks. When prednisone was down to 5 mg/d, the patient developed gout that was treated with colchicine and allopurinol. Two weeks later, Scr was 3.4 mg/dL. Patient denied any rash. Allopurinol was discontinued, and prednisone (60 mg/day) was restarted, at which point his Scr had decreased to 2.5 mg/dL. CYP testing revealed the patient to be homozygous for inactivating polymorphism CYP2C19*2, which normally metabolizes lansoprazole. Patient was able to continue taking colchicine for gout without any adverse effect.

DISCUSSION

Cytochrome P450 (CYP) superfamily controls the most important pathway involved in phase I drug metabolism. These heme-containing microsomal enzymes are responsible for approximately 50% of the elimination of common drugs.[9] The genes encoding CYP enzymes are polymorphic, resulting in a high variability of drug excretion rates and final serum concentration among different individuals and ethnicities. A CYP family contains enzymes that share more than 40% of global sequence homology, whereas a CYP subfamily include family members that share more than 55% global homology.[10,11]

Individuals can be phenotypically characterized as extensive metabolizers (EM), ultra-rapid metabolizers (UM), or poor metabolizers (PM). The CYP poor metabolizer phenotype is defined by the presence of two decreased-activity alleles or loss-of-function alleles.[12] Individuals phenotypically characterized as PM have an important reduction in the metabolism levels of drugs that are substrates of those enzymes. This results in high levels of the drugs in serum, which can lead to an increase in pharmacological response and toxicity.

CYP2D6 is involved in the metabolism of many drugs, including antiarrhythmics, antihypertensives, beta-blockers, antidepressants, antipsychotics, neuroleptics, tamoxifen, codeine, and promethazine.[13] Table 1 provides a more detailed listing of drugs that are CYP substrates. CYP2D6*4 is the most common allele associated with the PM phenotype, with an allele frequency of 21% in Caucasians.[14] CYP2C9 metabolizes widely used drugs, including NSAIDs, phenytoin, losartan and S-warfarin[15] (see Table 1). CYP2C9*3 has been associated with the phenotype PM of losartan, warfarin, phenytoin, glipizide, and tolbutamide.[16] Finally, CYPC19 is responsible for

Table 1
Common substrates of CYP enzymes

CYP2D6	Alprenolol, amitriptyline, amphetamine, aripiprazole, atomoxetine, bisoprolol, bufuralol, carvedilol, chlorimipramine, chlorpheniramine, chlorpromazine, clomipramine, clozapine, codeine, cyclobenzaprine, debrisoquine, desipramine, dexfenfluramine, dextromethorphan, diazepam, disopyramide, dihydrocodeine, diltiazem, diphenhydramine, donzepil, dolasetron, doxepin, duloxetine, encainide, felbamate, flecainide, fluoxetine, fluphenazine, fluvoxamine, haloperidol, hydrocodone, imipramine, labetalol, lidocaine, loratadine, maprotiline, mephobarbital, methoxyamphetamine, metoclopramide, metoprolol, mexiletine, minaprine, mirtazapine, morphine, nebivolol, nortriptyline, ondaserton, oxycodone, palonosetron, paroxetine, perhexiline, perphenazine, phenacetin, phenformin, promethazine, propafenone, propranolol, protriptyline, risperidone, selegiline, sertraline, sparteine, tamoxifen, thioridazine, timolol, tolterodine, tramadol, trazodone, trimipramine, tropisetron, venlafaxine, zolpidem*
CYP2C9	Alosetron, amitriptyline, bosentan, candesartan, celecoxib, chlorpropamide, diclofenac, dronabinol, fluoxetine, flurbiprofen, fluvastatin, glibenclamide, glimepiride, glipizide, glyburide, ibuprofen, indomethacin, irbesartan, lornoxicam, losartan, meloxicam, montelukast, naproxen, nateglinide, phenobarbital, phenytoin, piroxicam, rosiglitazone, rosuvastatin, sulfamethoxazole, suprofen, tamoxifen, tolbutamide, torsemide, valsartan, warfarin†
CYP2C19	Amitriptyline, aripiprazole, carisoprodol, citalopram, clomipramine, clopidogrel, clozapine, cyclophosphamide, desipramine, desmethyldiazepam, diazepam, diphenhydramine, divalproex, doxepin, escitalopram, fluoxetine, imipramine, lansoprazole, mephenytoin, methadone, moclobemide, nelfinavir, olanzapine, omeprazole, pantoprazole, pentamidine, phenobarbital, phenytoin, progesterone, proguanil, propranolol, rabeprazole, ritonavir, sertraline, thalidomide, valproic acid, voriconazole, R-warfarin

*Coadministration of two or more of these drugs may further decrease the rate of elimination of any of the other drugs metabolized by CYP2D6.

†Coadministration of any of the foregoing may decrease the rate of elimination of other drugs metabolized by CYP2C9.

the metabolism of many drugs, including propranolol, proton pump inhibitors, phenobarbital, lansoprazole, and diazepam[17] (see Table 1). CYPC19*2 is the most common allelic variant associated with the phenotype PM.[18,19]

In this report, we describe two cases of acute renal failure in patients with inactivating polymorphisms CYP2D6*4, CYP2C9*3, and CYP2C19*2, which to the best of our knowledge are the first two cases of AKI associated with CYP deficiencies of cytochrome function. In Patient 1, in whom the AIN was biopsy-proven, the culprit medication(s) cannot be determined due to the number of different drugs administered at the same time. The patient had not been re-challenged with any of the above medications but did tolerate a course of cephalosporin several months later. The etiology of the AKI in Patient 2 is less defined. Unfortunately, because of thrombocytopenia during the first episode and a long holiday during the second episode, a renal biopsy could not be ascertained. Prednisone had to be started empirically. While AIN is definitely possible, other mechanisms could have played a role.[3] Response to steroids does not always mean the injury was due to AIN, as steroids are potent inducers of some isoforms of CYP.[20] Elimination of the offending drug could have been as important as suppression of the immune system.

The exact mechanism how renal injury results from inactive CYP polymorphisms has not been elucidated. One possibility is that the nephrotoxicity in increased due to the elevated levels. Although not conventionally accepted, overdosing may be a mechanism contributing to the development of AIN. Garibotto et al. reported a case of acute renal failure due to AIN following the ingestion of a self-prescribed mega-dose of noramidopyrine (metamizol) in a healthy man.[21] Goldsmith et al. reported another case of AIN secondary to an overdose of leflunomide.[22] In both cases, the AIN was felt to be related to the high serum levels of the drugs. The management of drug-induced AIN includes withdrawal of the potentially offending drugs and supportive therapy.[7] Recent data from Gonzalez et al. suggest that early corticosteroid treatment may improve the recovery of renal function and slow the progression to interstitial fibrosis.[23]

In conclusion, we report two cases where CYP deficiencies could have played an important role in acute kidney injury. More study is needed to further understand the role that cytochrome P450 plays in renal injury. Genetic testing should be considered when encountering patients with multiple drug intolerance or allergies. Whether this technology can be made sufficiently cost-effective so as to provide prospective illumination of pharmacotherapy in an era of personalized medicine remains speculative, but worthy of consideration.

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