CHAPTER 11

DRUG-INDUCED NEPHROTOXICITY

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The purpose of this article is to discuss the nephrotoxic effects of commonly used drugs in podiatric practice. Drug-induced nephrotoxicity accounts for approximately 20% of all acute kidney injuries (1). These drugs require special consideration prior to prescribing them. Acute kidney injury (serum creatinine increase of >0.5 mg/dl) has been associated with 6.5-fold increase in death, 3.5 day increase in hospital stay, and $7,500 in excess hospital costs for hospitalized patients (2).

VULNERABILITY OF KIDNEYS

Kidneys are highly vascular and receive 20-25% of resting cardiac output. Kidneys also excrete many drugs and are exposed to high concentrations of these agents. This combined with the kidney's ability to concentrate the filtrate exposes it to very high concentrations of the offending agent. The kidneys also metabolize some drugs and create even more toxic metabolites. Other drugs cause hemodynamic disturbances, leading to ischemia. Many of these acute kidney injuries are reversible by stopping the offending drug and initiating supportive therapy. If the offending agent is not stopped, it may lead to a chronic kidney disease state (3, 4).

PATIENTS AT RISK

Common risk factors for drug-induced nephrotoxicity are underlying kidney disease, age older than 60 years, diabetes mellitus, heart disease, intravascular volume depletion, and multiple nephrotoxic drugs. The risk of acute kidney failure increases with each additional risk factor (4). Although many patient-specific risk factors are outside of the physicians' control, there are some steps that can be taken to decrease the risk of drug-induced nephrotoxicity.

PREVENTION OF DRUG-INDUCED NEPHROTOXICITY

General preventative steps include: obtain baseline kidney function, decrease number of concomitant nephrotoxic drugs, ensure the patient is adequately hydrated, and adjust drug dose in patients with an underlying chronic kidney disease state. Obtaining a complete list of the patient's medications is paramount. Dehydration should be addressed prior to initiating therapy with a potential nephrotoxic drug and through the course of treatment (4).

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

NSAIDs are a diverse category of drugs and more than 20 drugs fall under this category. Over 111 million prescriptions are written for NSAIDs in the US annually and they account for approximately 60% of over-the-counter analgesics (5). The common mechanism of these drugs is the ability to decrease prostaglandin synthesis by inhibiting cyclooxygenase. NSAIDs are used commonly for analgesia, antipyretic and in large doses for anti-inflammatory purposes (5-8).

The function of prostaglandins in the kidney is to cause vasodilation. In hypovolemic states and in the setting of hypotension prostaglandin, synthesis is increased to maintain renal perfusion to minimize ischemia. This process is inhibited with NSAID use (7, 8).

The "triple whammy effect" is a combination of NSAIDs, angiotensin-converting enzyme (ACE) inhibitors and diuretics leading to renal impairment. As discussed previously NSAID use can impair the kidneys' ability to maintain efferent arteriole tone. ACE inhibitors can cause dilation of the efferent arteriole. These two mechanisms cause a decrease in glomerular filtration pressure, which is exacerbated further by diuretics, which reduce plasma volume leading to further decrease in real blood flow. The combination of these three drug classes impair the kidney's ability to respond to hypotension. This triad of drugs has been associated with greater than 30% increase in acute kidney injury. The risk is greatest at the start of treatment. NSAIDs should be used with extreme caution in combination with ACE inhibitors and diuretics (7, 8).

General prevention strategies include using the minimum effective dose of NSAIDs, decreasing the course of treatment, and avoiding usage of NSAIDs in patients taking ACE inhibitors, diuretics and those with an underlying chronic kidney disease. Alternative analgesic medications include acetaminophen, tramadol, and opioids (6-8).

ANTIBIOTICS

Antibiotic associated nephrotoxicity has been traditionally associated with aminoglycosides and vancomycin. Other classes of antibiotics implicated in nephrotoxicity include beta-lactams, sulfonamides, and fluoroquinolones (4). The focus of this article is vancomycin and trimethoprim/sulfamethoxazole (TMP/SMX).

Vancomycin is the first line treatment for methicillin resistant Staphylococcus aureus (MRSA) infections in hospitalized patients. Vancomycin has been implicated in nephrotoxic events since the early 1950s. Initial impurities in the manufacturing process gave it the nickname "Mississippi Mud." These impurities were likely the cause of the initially high nephrotoxicity rate. Since then the impurities have been removed and vancomycin induced nephrotoxicity ranges from 0-5% (9). Increased rates of nephrotoxicity have been reported with increased trough levels, longer duration of treatment, and when used in combination with other nephrotoxic drugs (9,10). Vancomycin induced nephrotoxicity is reversible in most cases and requires short term hemodialysis in 3% of patients experiencing nephrotoxic episodes (10).

TMP/SMX is an oral alternative to vancomycin for treatment of patients with MRSA infection. Trimethoprim has been well-documented to cause an artificial increase in serum creatinine without associated kidney injury (11). An acute kidney injury caused by TMP/SMX causes an increase in both BUN and creatinine. Multiple case reports demonstrate nephrotoxicity associated with TMP/SMX, but only one study (12) demonstrates incidence and severity of acute kidney injury associated with TMP/SMX. Fraser et al reported a 5.8% incidence of nephrotoxicity secondary to TMP/SMX administration compared to a control group receiving clindamycin, which saw zero incidence of acute kidney injury. The average time for kidney injury to occur was 8 days. The kidney injury resolved in all patients and only one patient required hemodialysis. Uncontrolled diabetics in the study were three times more likely to develop an acute kidney injury. Although this is just one study demonstrating kidney injury associated with TMP/SMX, the drug should be used with caution in patients with uncontrolled diabetes (12).

TREATMENT

Early recognition of a kidney injury is critical. Treatment for drug-induced nephrotoxicity is the same as other forms of acute kidney injuries. The offending drug(s) need to be stopped immediately. Hemodynamic stabilization via intravenous hydration is a priority in hypovolemic states. The vast majority of these patients do not require hemodialysis and recover once proper treatment has been initiated (1-4, 7-10, 12, 13).

In conclusion, potential nephrotoxic drugs should be used with caution especially in high risk patient populations. Multiple strategies exist for decreasing the potential for nephrotoxicity including adequate hydration, decreased length of treatment with nephrotoxic drugs, and avoidance of nephrotoxic drug combinations.

REFERENCES

1. Jha V, Chugh KS. Drug induced renal disease. J Assoc Physicians India 1995;43:407-21.
2. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 2005;16:3365-70.
3. Zager RA. Pathogenetic mechanisms in nephrotoxic acute renal failure. Semin Nephrol 1997;17:3-14.
4. Naughton CA. Drug-induced nephrotoxicity. Am Fam Physician 2008;78:743-50.
5. Conaghan PG. A turbulent decade for NSAIDs: update on current concepts of classification, epidemiology, comparative efficacy, and toxicity. Rheumatol Int 2012;32:1491-502.
6. Nderitu P, Doos L, Jones PW, Davies SJ, Kadam UT. Non-steroidal anti-inflammatory drugs and chronic kidney disease progression: a systematic review. Fam Pract 2013;30:247-55.
7. Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. BMJ 2013;346:e8525.
8. Loboz KK, Shenfield GM. Drug combinations and impaired renal function -- the 'triple whammy'. Br J Clin Pharmacol 2005; 59:239-43.
9. Hazlewood KA, Brouse SD, Pitcher WD, Hall RG. Vancomycin-associated nephrotoxicity: grave concern or death by character assassination? Am J Med 2010;123:182.
10. Van hal SJ, Paterson DL, Lodise TP. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. Antimicrob Agents Chemother 2013;57:734-44.
11. Kastrup J, Petersen P, Bartram R, Hansen JM. The effect of trimethoprim on serum creatinine. Br J Urol 1985;57:265-8.
12. Fraser TN, Avellaneda AA, Graviss EA, Musher DM. Acute kidney injury associated with trimethoprim/sulfamethoxazole. J Antimicrob Chemother 2012;67:1271-7.
13. Weir MR. Renal effects of nonselective NSAIDs and coxibs. Cleve Clin J Med 2002;69Suppl 1:SI53-8.