Just the Berries

Nephrotoxic drugs

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Many pharmaceutical agents can have nephrotoxic side effects. It would be impossible for general practitioners to remember them all. There are, however, a few drug classes used daily in general practice that have such serious adverse effects it is worthwhile remembering which ones they are.

Antibiotics

Antibiotics can cause renal failure through a variety of mechanisms, including direct toxicity to the renal tubules, allergic interstitial nephritis, and crystallization of the drug within the renal tubules.

Aminoglycosides can be nephrotoxic, and doses must be adjusted for patients with renal impairment. Even so, proper dose adjustment is no guarantee of safety.[1] Aminoglycosides are excreted solely in the urine and are directly toxic to proximal tubular cells. Once-daily dosing with aminoglycosides is convenient and could be less toxic for people with normal renal function,[2] but no data support once-daily dosing for patients with impaired renal function even if dosage is adjusted. Family physicians should avoid aminoglycosides completely for patients with renal insufficiency. If no suitable alternative is available for patients suspected of having life-threatening Gram-negative bacteremia, a single 1.5-mg/kg dose of an aminoglycoside would be considered safe and would allow time to consult with an infectious disease expert (level V evidence).

Allergic interstitial nephritis, an idiosyncratic reaction, can be a side effect of many drugs. Antibiotics are by far the most common culprits. You cannot prevent interstitial nephritis; you can only recognize the syndrome promptly and discontinue the offending agent. Ongoing fever, rash, progressive renal failure, and eosinophilia during prolonged antibiotic therapy should suggest interstitial nephritis, which can be confirmed by renal biopsy. Although penicillins and cephalosporins are well recognized causative agents, almost any antibiotic can be the cause. The fluoroquinolone ciprofloxacin is now a well recognized cause of allergic interstitial nephritis (level III evidence).[3]

Crystallization of antibiotics in the renal tubules can lead to acute oliguric renal failure and has been reported with sulfa drugs, acyclovir, and indinavir (used to treat HIV infection). Although adequate hydration can prevent it, risk is increased substantially in the low glomerular filtration rate state of chronic renal insufficiency.[4] Adjusting the dose of sulfa drugs for patients with renal insufficiency is recommended, but does not guarantee safety. Although renal function can be restored after discontinuation of sulfa, patients are sometimes rendered permanently dependent on dialysis. It is best to avoid sulfa drugs for patients with renal insufficiency. Trimethoprim alone is as effective as combination therapy with trimethoprim-sulfamethoxazole for uncomplicated urinary tract infections (level I evidence).[5]

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Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors

These two classes of drugs have similar safety profiles for patients with renal insufficiency (level III evidence). Both can cause edema, hypertension, congestive heart failure (CHF), and acute or chronic renal failure.[6] Effects are dose dependent and usually reversible, although patients with advanced renal failure can become permanently dependent on dialysis. Suitable alternatives should be sought wherever practical. Acetaminophen is by far the safest analgesic for patients with renal failure (level V evidence).

In the past, combinations of acetaminophen and other analgesics were thought to be responsible for analgesic nephropathy, but acetaminophen alone in recommended doses is rarely nephrotoxic (except when combined with alcohol).[7] Colchicine (dose adjusted for renal impairment), joint injection, and brief courses of systemic corticosteroids are better tolerated than nonsteroidal anti-inflammatory drugs (NSAIDs) for episodic gout in renal insufficiency.[8] If an NSAID is absolutely required, use the lowest dose necessary for controlling inflammation for the shortest period possible and monitor patients closely for edema, hypertension, CHF, and renal function (level IV evidence).

Angiotensin-converting enzyme inhibitors and adrenergic receptor binders

These classes of drugs have been immensely successful for managing cardiovascular disease, hypertension, and chronic nephropathy. Large clinical trials of stable outpatients showed the drugs were extremely well tolerated, but none of these trials included patients with advanced renal failure (creatinine levels >300 µmol/L).[9] Initiation of angiotensin-converting enzyme inhibitors and adrenergic receptor binders (ACE/ARB) in patients with advanced renal failure can precipitate uremia, hyperkalemia, and dialysis dependence. Physicians are advised to refer these patients to nephrologists before initiating ACE/ARB therapy (level IV evidence).

Previously stable patients taking chronic ACE/ARB therapy can become dehydrated and develop profound renal failure that requires temporary dialysis. Volume depletion often mandates withdrawing ACE/ARB therapy; it can be reintroduced successfully once euvolia is established. Although bilateral renal artery stenosis has been considered a contraindication to ACE inhibitors in the past, renovascular disease is often associated with severe hypertension that responds well to blockage of the renin-angiotensin system.[10] In high-risk patients, blood pressure, creatinine, and potassium should be carefully monitored when initiating or increasing the dose of these drugs. Some mild elevation in serum creatinine is acceptable to get the benefits of ACE/ARB. Some authors have argued creatinine levels could be allowed to rise 30%, as long as they stabilize and patients have no symptoms of uremia[11] (level IV evidence).

Lithium

Lithium therapy for bipolar affective disorder has long been associated with a variety of renal abnormalities, including nephrogenic diabetes insipidus, chronic interstitial nephritis, and minimal change glomerulonephropathy.[12] By far the most worrying is progressive renal failure in association with interstitial nephritis. Whether lithium is the causal agent is unclear; the relationship might simply be an association since patients with chronic psychotic disorders not treated with lithium are also at higher risk of chronic interstitial nephritis[13] (level III evidence). Withdrawing

lithium therapy can have disastrous consequences and should be done only under the supervision of physicians experienced in managing bipolar affective disorder.

Intravenous contrast dye

High-molecular-weight or ionic contrast dye can cause severe vasospasm in the afferent arteriole and acute renal failure in susceptible patients. Risk factors include diabetes, myeloma, chronic renal failure, dehydration, diuretic therapy, and CHF.[14] Vasospasm is less common with newer lower-molecular-weight or nonionic contrast dye (level I evidence).[15] Hydration with intravenous saline is the simplest way to reduce contrast nephrotoxicity (level I evidence),[16] and use of prophylactic acetylcysteine can also reduce it (level II evidence).[17] It remains unclear whether these measures can prevent acute tubular necrosis in extremely high-risk patients with advanced renal failure. The best way to prevent vasospasm is to avoid contrast dye altogether by using ultrasound, magnetic resonance imaging (gadolinium enhancement is not nephrotoxic),[18] or unenhanced computed tomography scans for high-risk patients (level III evidence).

Conclusion

If physicians avoided NSAIDS, cyclooxygenase-2 inhibitors, sulfa drugs, aminoglycosides, and intravenous contrast dye in patients with renal insufficiency, they would rarely see cases of drug-induced renal failure, except for dehydration associated with ACE/ARB therapy.

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