Kidney news
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DRUGS & NEPHROTOXICITY

Many prescription drugs have been associated with renal injury. The mechanisms are not fully understood in many cases. Some reactions are presumed to be primarily immune-response mediated (e.g. quinolones, NSAIDs and gold) and some direct toxicity (NSAIDs, lithium). As the interstitium of the kidney is the water conservation and concentrating region of the kidney, it is not surprising drug toxicity is common here, expressed as **interstitial nephritis.**

Whether or not a high fluid intake to ensure maintenance of a high urine output (to minimise the time a toxic agent has in the interstitium) has any effect on reducing toxicity to the interstitium is only theory.

The table below lists common prescribed medications that are identified as causing renal injury, and the documented or suspected injury.

Drug	**Injury**
Gold salts	Membranous nephropathy
D-penicillamine	Membranous nephropathy
NSAIDs	Minimal change nephropathy, interstitial nephritis
Lithium	Minimal change nephropathy, FSGS, interstitial nephritis
Quinolones	Minimal change nephropathy, interstitial nephritis
Pamidronate	Minimal change nephropathy, FSGS
Omeprazole, Lansoprazole, Cimetidine	Interstitial nephritis
Bezafibrate	Interstitial nephritis
5-aminosalicylates	Interstitial nephritis
Penicillins	Interstitial nephritis
Cephalosporins	Interstitial nephritis
Allopurinol	Interstitial nephritis

The toxicity of the drug is idiosyncratic and time course of onset often not predictable. Prolonged use of the potential agent may result in no damage at all (e.g years of NSAIDs therapy for osteoarthritis analgesia); and yet a few days of ciprofloxacin (for example, but not restricted to ciprofloxacin) may lead to marked interstitial nephritis with severe renal failure.

Prolonged interstitial nephritis will result in fibrosis; loss of nephrons and GFR. Persistent insult with the medication may well progress to CRF. Nephron loss may result in secondary FSGS (see June 2006 newsletter); and progressive renal failure to end-stage.

Cessation of the suspected offending agent and following renal function regularly is often all that is required in the early phases. Renal function may return to normal. Once there is established renal failure, often from nephron loss or interstitial fibrosis, renal function regained is minimal.

Who should be monitored?

It is not practical to monitor every patient's urine (MSU) and renal function (serum creatinine) with the initiation of any potentially toxic medication.

Initiation of ACE inhibitors or ARBs are often associated with a small rise in the creatinine/loss of GFR (usually less than 20%); and most people would test for a change in creatinine or GFR of >20% on initiation of the first use of one of such agents. This loss of renal function is especially important to look for in patients with other evidence of vascular disease (e.g. coronary, cerebral and peripheral vascular disease).

Some situations that should raise an awareness to check renal function when commencing a renally toxic agent:

1. **Previous nephrotoxicity** with other agent. It is possible in immune-mediated situations the individual patient may have a predisposition to such hyperimmune responses to subsequent agents.
2. **Pre-existing renal dysfunction**. The amount of renal tissue to deal with the nephrotoxic agent is reduced, and may predispose the patient to a higher risk.
3. **Combinations of nephrotoxins**. The theory being two nephrotoxins may tip the balance of the kidney's ability to cope. E.g. a patient on bezafibrate for sometime, then has NSAID added for pain. Such a case may well deserve a close watch on their renal function.
4. **Elderly**. Renal function deteriorates with age; and the elderly are running on a reduced nephron load. They are similar to situation 2 above.

Screening and monitoring of nephrotoxicity

Serum creatinine and MSU are adequate screening. Nephrotoxicity will present with either reduced renal function or abnormality in the urine - typically proteinuria, WBCs (often eosinophils in interstitial nephritis), or RBCs.

The development of interstitial nephritis or toxicity can be variable with each agent and idiosyncratic within the individual; making the recommendation of frequency of testing difficult.

Rapid onset of renal toxicity will occur within weeks; and 1-2 tests of MSU and creatinine in the first month should be adequate to detect early.

The more insidious onset of nephrotoxicity could take months to manifest.

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I recommend in such situations, three monthly renal monitoring (blood creatinine and MSU) tests for a year; and once or twice per annum thereafter is a reasonable attempt to detect medication nephrotoxicity. This may not detect every case, every time; however I consider a reasonable balance of effort and pragmatism.

A difficult confounding issue is OTC medications and complementary or alternative therapies that may be nephrotoxic. Sometimes the patient will not report the use of such agents, as they feel they are not prescribed and therefore "not important".

Commonly used compounds that are occasionally associated with renal effects or nephrotoxicity include: Juniper (used for gout or as a diuretic); Ginseng (exacerbates hypertension); St John's Wort (interstitial nephritis). Although not proven there are a few cases of interstitial nephritis in patients using glucosamine and/or chondroitin. For more see appendix F of www.kidney.org.au/cari/drafts/new/nut_appendices.html

What to do after screening abnormality is identified?

In most cases ceasing the suspected agent and monitoring for recovery once or twice per month is adequate. In most acute cases the reduced GFR or urine abnormalities will resolve within weeks. More chronic cases may take several months, if ever. Referral is appropriate if there is not improvement within a three months after ceasing the suspected agent; sooner if there is further GFR loss.

Should the suspected agent be ever re-prescribed?

Generally an alternative should be sought: for example pantoprazole or ranitidine in place of omeprazole.

In some clinical situations there is no other agent suitable, e.g. lithium in manic-depression; and patient awareness and education are a must. A calculated risk is entered into; and such a case decision will require the input from GP and family, psychiatrist and renal physician. As long as the patient is well aware of the potential consequences (of which end-stage renal failure is the possible severe end-point) and is prepared to risk this on balance of therapy benefits against risks, therapy can be recommenced.

Wherever possible an alternative therapy or medication should be investigated in the first instance.

Summary

Nephrotoxicity from prescription medications is an uncommon problem; and very rarely results in severe consequences (end-stage renal failure). Serum creatinine and MSU are adequate screening tests. A serum creatinine and MSU every time a patient is commenced on a potentially nephrotoxic agent is NOT indicated.

Awareness of higher risk groups (e.g. elderly, previous nephrotoxicity, pre-existing renal impairment and combination of potentially nephrotoxic agents) is the key to considering early detection screening and monitoring for renal damage.

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Special Interests

Investigation of renovascular disease and hypertension
Management of urinary tract infections
Investigation of urinary calculi
Investigation of proteinuria and haematuria
Early detection, investigation and management of impaired renal function; and eGFR.
Renal nutrition.

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