Acute Pain in Renal Failure:

What is the Role of NSAIDs?

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Presented at the University of Calgary Resident Research Day, Calgary, Alberta, April 19, 2007.

NSAIDs are very effective analgesics. They are available in OTC and prescription formulations. They are used to treat renal colic with good effect. However, what is their safety in the setting of a patient with mild renal impairment?

NSAIDs have been associated with two types of renal dysfunction. The first, hemodynamically mediated acute renal failure (ARF), is due to NSAID inhibition of prostaglandin synthesis that can lead to renal ischemia and ARF. This is especially important in states of volume depletion where prostaglandin production increases in order to maintain renal blood flow and preserve glomerular filtration. The second, known as acute interstitial nephritis with or without nephrotic syndrome, is believed to be due to the preferential conversion of arachidonic acid to leukotrienes which cause minimal change disease in the kidney and nephrotic symptoms in the patient. The latter is very rare (< 0.1%) in NSAID users.

The literature evaluating the risk of inducing renal failure from NSAID use is quite limited. Most of the studies are nested case-control studies in people > 50-years-of-age. Each study has different end point parameters and definitions of ARF. Multiple risk factors were identified and are important considerations in whether NSAID therapy is appropriate.

Rafi's case

Rafi, 65, has had worsening right flank pain for 6 hours. He is unable to find a comfortable position. He denies having a fever, chills, vomiting or diarrhea. There is no gross hematuria. He has had so much discomfort that he has been eating and drinking very little.

His vitals are stable and he is afebrile. The physical exam reveals right costovertebral angle tenderness. His labs are remarkable for > 3 red blood cells on urinalysis and a creatinine of 176 µmol/L. He is requesting something to take away his pain.

Rafi's diagnosis and treatment dilemma

Rafi has renal colic. He has hypertension and is currently on hydrochorlothiazide and ramipril. He has never been told that he has any "kidney problems." He has been taking some ibuprofen that his wife had at home over the last two days for this pain. Otherwise, he only takes his BP medications.

Rafi's elevated creatinine is multifactorial. It may be due in part to his volume depleted status. He may have some mild impairment from his hypertension. How much is related to his recent NSAID use and will his renal function be further impaired if he receives more NSAIDs to control his renal colic?

Read on for the answers...

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Risk factors for ARF in NSAID users (Table 1)

Dosage

Risk is dose dependent: the higher the dose of NSAID, the risk of developing ARF can be two to four times the nonuser. For example, naproxen doses > 750 mg q.d. had twice the adjusted rate ratio of developing ARF than doses < 750 mg q.d.

Course of therapy

The highest risk of developing ARF is within the first 30 days of use. After that time, the risk remains elevated but less than that of the initial period. Once the NSAID is discontinued, the risk of ARF returns to baseline after 30 to 60 days without use. The longer the therapy is continued the higher the risk overall.

Drug interactions

It was shown in the studies that NSAID use with antihypertensive medications increased a patient's risk of ARF from five to 10 times that of NSAID use alone. Diuretics, ACE inhibitors, calcium channel blockers and ß-blockers were considered and diuretics had the most consistent negative impact on outcomes.

Independent risk factors

Male gender and increasing age added to the overall risk. Interestingly, CV comorbidites including hypertension, coronary artery disease and diabetes induced a 4.5 increase in relative risk of ARF which was worsened by concomitant ASA use. Recent hospitalization for nonrenal illness also negatively impacted outcomes.

Table 1

Risk factors for NSAID-related acute renal failure

- Dose
- Other NSAID use
- ASA use
- Duration of therapy
- Other medications, especially nephrotoxic drugs
- Male gender
- Age
- CV comorbidities
- Recent hospitalizations for nonrenal illness

Take-home message

- Assess risk factors
- Arrange for close monitoring of renal function, electrolytes, peripheral edema and BP in first month of therapy
- Use lowest possible dose for shortest period of time
- Have low threshold for discontinuing therapy if concerned
- Review patient's medications to reduce risk of drug interactions

Conclusions and recommendations

NSAID induced ARF or the potential for this to occur is an important consideration when prescribing or recommending this therapeutic option. It is very necessary to assess the risk factors that may increase the risk of the development of ARF. Furthermore, close follow-up in a patient, especially one on an extended course of therapy, should monitor for signs of worsening hypertension, development of hyperkalemia or any signs of the onset of nephrotic complications. The lowest dose for the shortest duration is the safest. Any therapy should be discontinued in the setting of an increasing creatinine, signs of nephrotic syndrome or ARF. Dx

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