Adverse effects of NSAIDs on renal function

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The effects of use of nonsteroidal anti-inflammatory drugs (NSAIDs), analgesic compounds effective in treating a wide range of musculoskeletal disorders, are attracting increasing attention. Many drugs are overprescribed, and many patients consume excessive amounts of analgesic, laxative or psychoactive drugs, but the magnitude of the use of NSAIDs is almost incredible. Each day well over five million people in the United States take NSAIDs, and this figure does not include those taking other inhibitors of prostaglandin synthesis, such as salicylates; as many as 36 million Americans may have taken NSAIDs at some time.[1]

Because of the potential market many types of NSAIDs have appeared. For the most part they are indistinguishable in activity and in adverse effects. With such a large exposure, reporting of adverse side effects is inevitable, but assessment of the significance of such effects is difficult since few studies have identified the true incidence of a given complication within an identified population taking the offending medication. Some of the reported side effects have been dramatic, necessitating removal of individual drugs from the market, and in some cases the importance of side effects has been overplayed, given the evidence available. The removal of benoxaprofen (Opren) from the market in the United Kingdom led to a major television inquiry into marketing practices and the responsibility of the medical profession in postmarketing surveillance. The inquirers severely criticized rheumatologists who were filmed enjoying a trip to Venice funded by the maker of another new NSAID and the academic community for less than meticulous objectivity in reporting studies funded by pharmaceutical companies.[2] All of this underscores the necessity of vigilance in identifying and recording the effects of drugs and in collecting accurate data to allow fair evaluation of risk/benefit ratios.

The committee on drugs and pharmacotherapy of the Ontario Medical Association (OMA) has established a program for reporting adverse reactions to drugs, and in February 1983 it issued a warning to the medical profession about the hazards of NSAIDs.[3] Although a laudable attempt to focus attention on the problem of reactions to drugs, this type of reporting and data collection has many drawbacks. Some of these drawbacks, such as the lack of information on the true incidence of reactions (related to population at risk) and the tendency to report reactions to newer drugs more frequently, have been acknowledged by the committee.

An update from the committee[4] documented further reports of reactions to NSAIDs. Hospital pharmacists submitted over half of the reports received, and physicians only 30%. NSAIDs were responsible for 10% of all the adverse reactions reported, 53% of which were considered "serious". Virtually all of the serious reactions were episodes of gastrointestinal bleeding, with or without proven peptic ulceration. Most such reactions could not have been missed, particularly since the gastrointestinal side effects of NSAIDs are now widely known and are acknowledged in package inserts and advertising material.

The reporting system has not, however, identified the less well known, but potentially as dangerous, side effects of NSAIDs on renal function, electrolytes and blood pressure. There have been many recent reports of renal impairment after treatment with NSAIDs;[5] of course, these findings contain the same deficiencies as those on gastrointestinal side effects. Nevertheless, many nephrologists now feel that NSAIDs are responsible for a large percentage of drug-induced renal damage as well as electrolyte disturbances and difficulties with control of blood pressure.

A variety of adverse effects of NSAIDs on renal function have been identified.

- Reduction in renal blood flow and the glomerular filtration rate.
- Acute tubular necrosis.
- Allergic interstitial nephritis, with or without accompanying nephrotic syndrome.
- Renal papillary necrosis.
- Water, salt and potassium disturbances.
- Impairment of blood pressure control.

Renal blood flow and the glomerular filtration rate

Most of the actions of NSAIDs are probably related to inhibition of cyclo-oxygenase and, therefore, reduction of prostaglandin production. That interference with

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prostaglandin synthesis might affect renal function is not surprising, since prostaglandins probably play a major role in mediating changes in renal perfusion, although the nature of these effects and their relation to other vasomotor systems have not yet been fully worked out. Infusion of most prostaglandins into the kidneys of experimental animals produces increases in renal blood flow, but only if pharmacologic doses are used. NSAIDs have been shown to reduce renal blood flow in anesthetized animals but not in intact, conscious dogs.[6]

There is little evidence that inhibition of prostaglandin production has any effect on renal blood flow or the glomerular filtration rate in healthy humans. It is likely, however, that NSAIDs predictably and uniformly reduce renal blood flow and the glomerular filtration rate in patients in whom renal perfusion is stressed by other factors, such as pre-existing renal disease or reduced effective blood volume. Clinical evidence suggests that in patients who are receiving diuretics or who have cirrhosis, nephrotic syndrome, cardiac failure, renal impairment, a salt deficit or systemic lupus erythematosus NSAIDs usually produce a decrease in the glomerular filtration rate and an increase in the serum creatinine level.[7] This is usually reversible with cessation of therapy but may progress to full-blown acute tubular necrosis, necessitating dialysis. Even though the reduction in renal function is reversible, the cause of renal deterioration in these patients may not be identified, or the deterioration may be attributed to the underlying disease; thus, the reduction in renal function may contribute significantly to morbidity and mortality.

Since the glomerular filtration rate decreases with age the use of NSAIDs may pose a special risk in the older patient, particularly if given in combination with a diuretic.

Allergic interstitial necrosis

Renal function may also be impaired by NSAIDs by an entirely different mechanism. All of these drugs have on occasion produced classic allergic interstitial nephritis, usually presenting as acute renal failure, often nonoliguric. In many of these cases the lesion is clinically and pathologically indistinguishable from that produced by other, unrelated drugs, particularly antibiotics and diuretics,[8] but there are also over 20 reports of the concurrent appearance of allergic interstitial nephritis and a nephrotic syndrome characterized histologically only by effacement of the foot processes in the glomeruli.[1] This combined lesion seems to be almost specific to NSAIDs, and it has been suggested that it may be due to uncontrolled production of lymphokines from sensitized T lymphocytes.[9] Both the interstitial nephritis and the nephrotic syndrome usually resolve with withdrawal of the offending drug, with or without steroid therapy.

Renal papillary necrosis

NSAIDs seem to have contributed occasionally to episodes of acute renal papillary necrosis, usually in the presence of underlying renal disease.[8] Anecdotal reports have attributed episodes of hypersensitivity vasculitis and cutaneous vasculitis to these drugs, but the frequency of these complications is very low.[8]

Water, salt and potassium disturbances

NSAIDs affect water and electrolyte metabolism. A small degree of fluid retention commonly occurs but seldom presents a clinical problem. The most important and potentially dangerous electrolyte disturbance is hyperkalemia, sometimes of life-threatening severity. This may be due to hyporeninemic hypoaldosteronism, since it is known that NSAIDs suppress renin production, particularly in patients with pre-existing renal disease, but it may also be due to changes in transcellular potassium transport.[5]

Impairment of blood pressure control

NSAIDs are known to reduce furosemide-induced natriuresis and to reduce the antihypertensive effects of diuretics, β-blockers and captopril. They have no significant effect on blood pressure in healthy people but in hypertensive patients have been shown to reduce the effects of antihypertensive drugs by as much as 50%.[10]

Warnings about drug-induced renal damage are written in very small print, if at all, on the package inserts of most NSAIDs. The reports of the OMA committee on drugs and pharmacotherapy[3,4] might be interpreted as providing support for this, since severe renal damage does not even rate a mention. What interpretation, then, should be placed on the concern shared by many over renal damage and the evidence I have reviewed?

Interstitial nephritis, nephrotic syndrome and vasculitis probably represent allergic phenomena that may be caused by many drugs and that occur in only a very small proportion of the vast numbers of patients taking NSAIDs. Concurrent interstitial nephritis and nephrotic syndrome is of great academic interest, holding the tantalizing possibility of a clue to the pathogenesis of minimal change disease, but it certainly is so rare as to have no impact on decisions whether to use NSAIDs. The risk of hyperkalemia seems definite, but it usually exists in patients with pre-existing renal disease, whose potassium level would be monitored anyway. The risk of loss of blood pressure control simply needs to be more widely known; it should seldom present a major clinical problem.

Reduction in renal blood flow and the glomerular filtration rate, however, may be a different matter. There is a possibility that a high-risk group can be identified: NSAIDs do not impair renal function in healthy people, but they do in people with renal disease or a reduced effective blood volume, apparently fairly uniformly. Clinical evidence of renal disease, reduced liver function or congestive cardiac failure, or any evidence of reduced blood volume identifies patients in whom, at the very least, renal function should be carefully monitored if NSAIDs have to be prescribed. This group may include all patients with a high plasma renin level, which indicates some stress on renal perfusion. Further study of patients at risk should allow the incidence of transient renal impairment and acute tubular necrosis to be identified and then reduced.

One NSAID, sulindac, may not have this adverse effect on renal function, but this certainly requires further study.

It is not known whether the reductions in the glomerular filtration rate induced by NSAIDs are dose related, since there are reports of very small doses inducing renal impairment.[5] It is also not known whether patients receiving two or more NSAIDs are at increased risk, although there is evidence suggesting that patients exhibiting renal injury due to phenylbutazone are more sensitive to further damage from other, chemically distinct NSAIDs.[5]

Large numbers of patients will continue to require and benefit from NSAIDs in the treatment of musculoskeletal and rheumatic ailments. However, the possibility of renal impairment should always be considered, and the renal function of patients whose function may already be stressed should be evaluated after a few days of treatment. The adverse effects of NSAIDs on renal function are less clamant than the gastrointestinal effects but are probably as dangerous, are less easily identified and are potentially avoidable or reversible if care is taken.

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