CHAPTER 36

USE OF ANALGESICS IN PATIENTS WITH RENAL DISEASE

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The podiatric surgeon is routinely faced with the dilemma of postoperative analgesia in surgical patients. This can be accomplished by a myriad of drugs, both narcotic and non-narcotic analgesics. This decision is more complicated for those patients who have renal impairment, either chronic renal disease (CRD) or end-stage renal disease (ESRD). Due to increasing life-span and the specific, at-risk population routinely encountered by the podiatric surgeon, renal insufficiency has become a more frequent occurrence, and therefore, a basic understanding of the disease process and medications which can be safely administered is absolutely essential. Because the patient with renal insufficiency is unable to metabolize medication normally, care must be taken when choosing an appropriate analgesic, along with extremely careful observation to see that the medication is being tolerated well without causing serious side effects. Although most analgesics are metabolized predominantly by the liver with renal excretion contributing little to the overall elimination, analgesics can be hazardous to the patient with renal disease.[1]

Analgesic medications can be broadly divided into non-narcotic and narcotic categories. Common non-narcotic analgesics include aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs (NSAIDs). Frequently-used narcotics include morphine, codeine and its derivatives, meperidine, tramadol, pentazocine, and propoxyphene. This article will review common analgesics and their effects on the patient with renal insufficiency.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

A large number of nonsteroidal anti-inflammatory drugs (NSAIDs) are currently prescribed including Ibuprofen (Motrin, Advil, Nuprin), Indomethacin (Indocin), Naproxyn (Naprosyn), Sulindac (Clinoril), and Piroxicam (Feldene), Piroxlcam (Feldene), Celecoxib (Celebrex) and Rofecoxib (Vioxx). Side effects related to the drug's mechanism of action requires that caution be used in prescribing these agents to patients with renal problems.[1] NSAIDs produce their analgesic effect by reversible inhibition of prostaglandin synthesis. This is done by preventing the oxidation of the most common prostaglandin precursor, arachidonic acid.

Prostaglandins are involved in renin release, local vascular tone, regional circulation, sodium and water homeostasis, and potassium balance. In normal individuals, prostaglandins are not primary mediators of basal renal function. They typically operate in conjunction with a variety of other mediators, which, when in the absence of prostaglandins, can preserve homeostasis.[2] However, under conditions associated with impaired renal blood flow, prostaglandins are critical in maintaining adequate perfusion of the kidney. Clinical conditions in which this occurs include renal insufficiency of any cause, congestive heart failure, nephrotic syndrome, cirrhosis, hypovolemia, and advanced age. When patients with these problems are given NSAIDs, renal function can acutely deteriorate, as the beneficial effects of prostaglandins on renal perfusion are blocked.[1]

The addition of NSAIDs increases the risk of azotemia and possibly ischemic damage to the kidneys by removing the protective effects of vasodilatatory prostaglandins and allowing unopposed vasoconstriction.[2] Initially, this NSAIDs-induced renal syndrome is of moderate severity and is characterized by increased BUN, creatinine, potassium, and weight with decrease urine output. NSAIDs-induced acute renal failure is usually reversible over 2 to 7 days after discontinuation of therapy; however, morbid consequences can occur if the diagnosis is not recognized early. Continued NSAIDs therapy in the presence of deteriorating renal function may result in rapid and progressive deterioration to the point where dialysis support is required.[3] Despite this profound level of renal function impairment, the kidney will nonetheless recover several days to weeks after discontinuation of the NSAIDs.[2]

Patients with chronic renal impairment are at increased risk of NSAIDs-induced renal failure

because of inadequate renal prostaglandin production. Therefore, these drugs should be avoided when possible in patients with predisposing disorders. When NSAIDs must be prescribed for patients with these problems, close observation of renal function is mandatory. NSAIDs also have two other potential side effects which have particular significance for these patients. First, they are gastric irritants. Uremic patients are predisposed to gastritis, and these drugs undoubtedly enhance the potential for this complication. Secondly, NSAIDs inhibit normal platelet function and can worsen the bleeding defect associated with uremia.[1] Thus, one must be cautious when prescribing these drugs to patients with significant renal impairment. Lastly NSAIDs routinely cause fluid and electrolyte disturbances in the form of fluid retention and hyperkalemia. These side effects must also be closely monitored in patients with renal insufficiency to prevent severe complications.[3]

The selective Cox-2 inhibitors, celecoxib and rofecoxib do not offer distinct advantages over the other non-selective NSAIDs with respect to renal regulation. Selective Cox-2 inhibitors, like other NSAIDs, must be used cautiously in patients with renal disease.[4]

ASPIRIN

Aspirin is effective in the treatment of mild pain, and can generally be used in modest doses in renal failure without dose adjustment. However, since its method of action is similar to that of NSAIDs, it shares all the potential side effects that are related to prostaglandin inhibition. Moreover, since aspirin binds to platelets irreversibly, the possibility of bleeding disturbances is greater. Because of this, the choice of aspirin for use as analgesia in renal insufficiency should generally be avoided.[1]

ACETAMINOPHEN

Acetaminophen is also a mild analgesic, but unlike aspirin and NSAIDs, possesses no anti-inflammatory activity, since its mechanism of action does not appear to involve inhibition of prostaglandin synthesis. It does not share the side effect profile of aspirin or NSAIDs. Acetaminophen requires no dose adjustment in renal failure and can be safely prescribed to patients with end stage renal disease. However, in very large doses or when taken in combination with aspirin or NSAIDs, acetaminophen is nephrotoxic.[1]

NARCOTIC ANALGESICS

Opioids produce an analgesic effect by sterospecific interaction with opioid receptors. The adverse effects of the opioid analgesics include mental obtundation, respiratory depression, and hypotension. The nonspecific reversible depression of central nervous system function by drugs is described by the term narcosis. Reversal of narcosis by administration of naloxone, an opioid antagonist, is evidence of opioid intoxication.[5] Hepatic biotransformation has been considered the primary route of elimination of opioids; however, the accumulation of active metabolites that are excreted mainly by the kidney pose a risk for those patients with renal insufficiency. In addition, several reports have documented prolonged narcosis in patients with renal failure receiving conventional regimens of narcotics, which do not require renal elimination.[5]

Morphine

Hepatic biotransformation has generally been considered the main route of elimination of morphine. Although renal clearance is generally considered unimportant for its elimination, recent evidence that kidney dysfunction may affect the disposition of or patient sensitivity to morphine. Several reports have suggested that patients with renal failure are more prone to develop adverse reactions to morphine than normal subjects.[5] A correlation between morphine clearance and creatinine has been reported, with the conclusion that renal function was an important determinant of morphine elimination.[6] Several studies on the pharmacokinetics of morphine in patients with renal failure demonstrate that the half-life of morphine is greatly prolonged, with elimination requiring days rather than hours. In addition, accumulation of the morphine metabolite, morphine-6-glucoronide (MGC), which is both pharmacologically active and excreted by the kidneys, may explain the reported increased sensitivity of renal failure patients to morphine.[7] Significant data clearly supports the need for major dose reduction of morphine with titration to the desired effect in the presence of renal failure. It is imperative that patients with renal insufficiency receiving morphine for postoperative analgesia be closely monitored for signs and symptoms of narcosis.

Codeine

Codeine is an opioid structurally similar to morphine. Metabolism of codeine occurs extensively by the liver; therefore previous early reports suggested that codeine could be used without specific dose reduction in patients with renal insufficiency.[1] Recently, however, there have been reports of codeine-induced narcosis. The elimination and clearance of codeine and its metabolites were noted to be prolonged in patients with renal insufficiency. The exact mechanism and pharmacodynamics are not completely understood at this time.[5] Even though the response in patients with renal failure to codeine does not appear to be as sensitive as morphine, care must be taken when prescribing this drug. Dose reduction, titration, and careful observation should be performed.

Oral derivatives of codeine (hydrocodone, oxycodone) are generally considered safe to use in patients with renal insufficiency. However, narcosis has been found to occur in some patients receiving normal doses of these medications.[5] In addition, these compounds typically are prepared with aspirin or acetaminophen. It is best to avoid those medications containing aspirin for the previously-mentioned reasons.

Meperidine (Demerol)

Meperidine is an opioid compound widely prescribed for its analgesic effects. It can be administered orally, IM or IV, and because it causes less constipation and urinary retention than morphine, it is a popular postoperative analgesic. Meperidine is metabolized in the liver, however, its metabolite, normeperidine, is excreted by the kidney. Normeperidine is half as effective as an analgesic agent, but twice as toxic.[8] The half-life of normeperidine is 15 to 20 hours. It is eliminated both by the liver and the kidney and can accumulate in patients with renal or liver disease. A study comparing meperidine use found that the ratio of normeperidine to meperidine levels was consistently higher in the patient with renal failure.[9] Accumulation of normeperidine occurs in patients with renal failure and causes seizures and other neuropsychiatric disorders.[1] One report documented the occurrence of delirium that resolved in 2-3 days following the cessation of meperidine. The patient had renal insufficiency and even though the dosage was greatly modified, narcosis still developed.[8] Because of normeperidine toxicity, meperidine should be avoided in patients with renal dysfunction.

Propoxyphene (Darvon, Darvocet)

Propoxyphene is structurally analogous to methadone, and is used to manage mild to moderate pain. Propoxyphene is primarily eliminated by N-demethylation to norpropoxyphene in the liver. Renal excretion of propoxyphene is insignificant but is the main elimination pathway for norpropoxyphene.[5] Both, propoxyphene and norpropoxyphene have been shown to depress cardiac conduction and their accumulation in the body can be dangerous. Although the central nervous system toxicities can be reversed with naloxone, naloxone is ineffective in managing the cardiac toxicities. Moreover, hemodialysis does not remove propoxyphene or its metabolite efficiently.[5] Thus, propoxyphene should be avoided in patients with advanced renal insufficiency.

Pentazocine (Talwin)

Pentazocine is primarily metabolized by the liver. It does not significantly accumulate in renal failure and can generally be used without dosage modifications in patients with renal disease. However, like other sedatives and narcotics, pentazocine may cause enhanced sedation in uremic patients. It can also precipitate acute behavioral disturbances in some patients (especially in the elderly) irrespective of renal function. Pentazocine is available in oral and parenteral forms and is a good agent for the acute or subacute treatment of moderate to severe pain in patients with renal dysfunction.[1]

TRAMADOL (ULTRAM)

Tramadol is a centrally active analgesic whose mechanism of action is not completely understood. Adjustment in the traditional tramadol dose is required in patients with renal or hepatic insufficiency because of the reduced rate of excretion seen in these patients. In patients with a creatinine clearance of less than 30 ml/min, the dose of tramadol should remain the same (50 to 100mg); however the dosing interval should be increased to 12 hours (instead of 4 to 6 hours) with a maximum daily dose of 200mg. Care must be taken when administering tramadol because it is poorly hemodialized, and treating tramadol overdose with naloxone may increase the risk of seizure.[10]

SUMMARY

Non-narcotic analgesics including Celebrex, Vioxx and asprin should be avoided in patients with renal disease. In view of reports of increased sensitivity of patients with renal failure to certain opioids, and the potential accumulation of active metabolites, a high index of suspicion of opioid-induced narcosis should be maintained when such patients receive opioid analgesics. Quick recognition of narcosis and prompt use of naloxone may prevent unnecessary patient morbidity. Empirical dosing for individual patients is warranted and dosage regimens should be titrated to response.[5] The discussion of these drugs has assumed that patients are healthy except for renal insufficiency. In particular, it has been assumed that hepatic function is intact. Also, uremic patients may still display enhanced sensitivity to sedatives and narcotics. Thus, sedation and respiratory depression may be more pronounced and may occur more frequently in patients with renal impairment who receive narcotics.[1] Postoperative analgesia in patients with renal insufficiency requires a thoughtful, stepwise approach. As always, a team approach with good communication between the podiatrist, the internist, and the nephrologist is imperative for the well-being and management of the renal patient.

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