Nonsteroidal anti-inflammatory drug use in the elderly: Issues of compliance and safety

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Many of the goals in caring for patients with non–life-threatening rheumatic conditions can be safely met with nonsteroidal anti-inflammatory drug (NSAID) therapy. These drugs relieve pain and stiffness and help to maintain joint mobility. However, no course of treatment can be successful without patient compliance. The difficulties of following dosage requirements and scheduling, together with the increased risk of adverse side effects, are particular problems for the elderly—the very patients who are the major consumers of NSAIDs. The key to successful NSAID therapy is maintaining patient comfort and function while using the simplest and safest medical regimen available. The author discusses ways in which these goals can be achieved.

(Key words: Elderly, arthritis, nonsteroidal anti-inflammatory drugs [NSAIDs], compliance)

Approximately one third of all adults in the United States have some symptoms of musculoskeletal disease.[1] These disorders range from relatively benign entities, such as bursitis and tendinitis, to life-threatening illnesses, including systemic lupus erythematosus, rheumatoid arthritis, and scleroderma.[2] Osteoarthritis is the most common rheumatic disease and its prevalence increases with advancing age.[1,3] The progression of this disease may lead to severe and permanent physical disabilities, including the inability to ambulate and to carry out other activities of daily living.

The primary goals in treating patients with osteoarthritis are relief of pain, maintenance of joint mobility and function, and lessening of joint swelling.[2] Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used to achieve these goals. An estimated 100 million prescriptions for NSAIDs were written in 1986 alone.[4] Developing an effective therapeutic regimen can be challenging, as there are clinical differences among the classes of NSAIDs. Moreover, wide variability exists in individual responsiveness to these drugs and their risk of adverse events.[4] *Table 1* outlines guidelines for the administration of NSAID therapy in the elderly.

A complicating factor is the ability of the patient to comply with the prescribed regimen. Compliance becomes a particular concern in the case of the elderly who comprise just 12% of the general population but consume 40% of all NSAIDs prescribed in the United States.[5]

In general, compliance with medications for rheumatic disease is directly related to pain: the more severe the patient's pain, the more compliance there will generally be with a given medication.[6] This may be the reason patients with rheumatoid arthritis are more compliant than those with osteoarthritis.[6] Therefore, the dosing and scheduling of NSAIDs usually should be titrated with symptoms. This titration gives the individual the opportunity to manage his or her own therapy more effectively. An alternative approach is to use a once-a-day NSAID. Eisen and associates[7] recently noted that patient compliance with antihypertensive medication improved from 59% on a three-times-per-day regimen to 84% on a once-daily regimen. Once-a-day dosing also allows the physician an almost immediate opportunity to evaluate both the effectiveness and the tolerability of the drug.

Precautions before initiating NSAID therapy

A thorough history and physical examination are essential in identifying patients at increased risk for adverse reactions to NSAID treatment. This is especially true for geriatric patients who often have age-related reductions in renal and hepatic function. In addition, they are more likely than

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younger patients to be receiving concomitant medications, thus increasing the chances of drug interactions. Also, because many older patients are on fixed incomes, the overall cost of therapy becomes important in NSAID selection.

When NSAID therapy is indicated, it is prudent to begin with the lowest recommended dose, gradually increasing the dose as necessary over a period of 2 to 4 weeks.[4] For the most part, low doses of NSAIDs are analgesic and high doses are anti-inflammatory. Because the type of arthritis found in the majority of elderly patients is osteoarthritis, pain control is of more concern than reduction of inflammation.

Patients often vary in their responsiveness to various NSAIDs and, after a few weeks, another NSAID—even within the same class—should be tried if the initial results are unsatisfactory. A move from one chemical class to another—such as changing from a carboxylic acid (diflunisal or aspirin) to a propionic acid (ibuprofen or oxaprozin)—may be recommended (*Table 2*). Although there is no good clinical evidence that any one NSAID is more effective than any other, some preparations may be better suited to a specific patient profile.[8]

Safety issues

Gastric ulcers have been found to occur in 10% to 15% of chronic NSAID users, and one third of these patients may be asymptomatic.[9] These problems increase in frequency with extended duration and increasing doses as well as with age.[8,9] Acute renal failure and hepatic insult are also well-documented side effects of NSAIDs. Dermatologic reactions (Stevens-Johnson syndrome), central nervous system disturbances (aseptic meningitis), hematologic conditions (neutropenia, aplastic anemia), and pulmonary disorders (hypersensitivity pneumonitis), although rare, are also potential side effects.[8] Some of these conditions have been associated with only a few of the NSAIDs.[12] Overall, the relative risk of adverse effects is low and should not routinely dissuade clinicians from prescribing NSAIDs for their patients.

If a patient is at increased risk for an adverse event or if one should occur unexpectedly, alternative therapy such as acetaminophen or propoxyphene can be used. If the reaction is not severe or life-threatening, a reduction in dosage or a change to another NSAID is a reasonable alternative if the therapy is carefully monitored.

Any patient who has gastrointestinal symptoms should have an initial complete blood cell count and a fecal occult blood test within the first month of NSAID use and every 3 to 6 months thereafter.[10] A history of cigarette smoking is also a significant factor in this subset of patients because of its association with peptic ulcer disease.

If NSAIDs are administered to geriatric patients with established renal insufficiency, it is suggested that serum sodium, potassium, blood urea nitrogen, and creatinine levels be measured within 1 to 3 weeks of initiation of therapy and every 3 to 6 months thereafter.[10] In patients at risk for hepatic toxicity—including many elderly patients with renal insufficiency, those using multiple drugs or alcohol on a regular basis, and those receiving a high drug dose—it is recommended that initial alanine aminotransferase levels be monitored within the first month of therapy and every 3 to 6 months thereafter.[10]

Some preparations are better suited to certain patient profiles. One newer NSAID, etodolac, is reported to have fewer gastrointestinal side effects because of its altered metabolism. This may be a suitable alternative in patients with a history of aspirin or NSAID-induced damage. Administration of NSAIDs with the synthetic prostaglandin analogue misoprosotol has the potential to reduce drug-induced gastric and duodenal ulcers.[11] However, misoprosotol must be taken four times daily, is associated with diarrhea, and compounds the overall cost of therapy.

Elderly patients receiving long-term NSAID therapy may be in danger of toxic drug accumulations because of a decrease in lean body mass together with reduced hepatic and renal function. An illustration of this is the systemic clearance of oxaprozin, an NSAID recently approved by the Food and Drug Administration. It is considered a low-clearance drug, which undergoes increased systemic clearance after large single doses and at steady state levels.[12] The strong binding of this drug to plasma protein—a characteristic common to all NSAIDs—is decreased at the higher concentrations found after a single large dose or after multiple doses when true steady-state is achieved.[13] The systemic clearance of oxaprozin helps to limit accumulation of the drug.[14]

Overcoming obstacles to compliance

Physical limitations

Although many older adults are in excellent gen-

Table 1
Guideline for NSAID Therapy in the Elderly

- **Dosing**
  - Low dose = analgesics
  - High dose = anti-inflammatory agents
  - Begin with lowest recommended dose indicated
  - Increase dose gradually
  - Use only as much drug as necessary to provide relief
- **Medication recommendations**
  - Obtain a thorough medical history
  - Perform a thorough physical examination to aid in evaluation for risk factors
  - Research which preparation is indicated for patient profile
  - Raise and address issues of less potent over-the-counter medications and warn against concurrent use with prescription NSAIDs
  - Initiate therapy with samples whenever possible
  - Consider switching to another NSAID if the patient does not respond initially
- **Suggestions for enhancing compliance**
  - Educate the patient regarding his or her disease state
  - Educate the patient regarding drug need and use
  - Consider once-a-day agents if appropriate
  - Provide patient with written prescription information, including how many pills to take how often
  - Always show the patient sample pills
  - Ask the patient to repeat dosing instructions
  - If patient's compliance with tablet form is unsatisfactory, try a liquid form
  - Enlist the help of family members, social workers, or visiting nurses in monitoring compliance
  - Encourage patient to be active and to walk daily

eral health, it is common for elderly patients to have several concomitant physical handicaps. According to one survey, 43% of patients older than 65 years are visually impaired and may be unable to accurately read dosage information on a bottle of a prescribed drug; between 25% and 45% are hearing-impaired and may not understand the physician's instructions; and as many as 10% have some neurologic dysfunction.[5] Moreover, concurrent cardiac or pulmonary diseases have been shown to significantly predict further disability with osteoarthritis.[8] These patients tend to be less physically active and are thus prone to decreased joint mobility and increased muscle weakness.

Patient education may help to overcome these potential barriers to compliance. The nature of the disease, as well as the purpose of the drug, should be fully explained.[6] All prescription information should be written clearly and concisely in easy-to-read handwriting or in large type.[5] The directions should be explicit in terms of how many "pills" are to be taken and when one is to take them. Having the patient repeat the medical advice and the rationale for use of the prescribed medication is often helpful. The patient should also be invited to ask questions and voice any concerns.

Memory failure

Elderly patients are frequently forgetful.[6] Even with written directions, compliance may be difficult. It has been shown that compliance is proportional to the number of pills the patient is expected to ingest. Compliance decreases to 60% or less when a drug must be taken more than twice daily. With single-dose therapy, compliance is 80% to 85%.[15]

Conversely, patients may become overly compliant and consume additional doses in the hope of attaining further pain relief. The danger of excessive ingestion of NSAIDs (especially those with a long half-life, such as piroxicam or nabumetone) is that circulating free drug levels of the NSAID will rise. The drug's half-life will be prolonged an additional 30% to 50%, and toxic levels may result.[4] This toxicity may be less of a problem with the newer NSAID oxaprozin for the reasons previously discussed.

It may be necessary to monitor the patient closely for overcompliance. Social workers, visiting nurses, and family members can aid in reinforcing the medication regimen.[6] One pharmaceutical company (G. D. Searle) has recently established a system whereby patients taking its product are called by telephone daily as a means of monitoring compliance.

Polypharmacy

Because of the availability of over-the-counter ibuprofen and soon-to-be-released naproxen, even otherwise compliant patients may be unknowingly overdosing themselves.[5] When the patient's medical history is being taken, the issue of over-the-counter drugs and self-medication should be addressed. All prescribed medications—especially oral anticoagulants and diuretics—should be reviewed. The potential for interactions with other drugs is believed to be increased in older patients who receive different medications for concomitant disease states. There is little evidence, however, that this in fact occurs.[14] Potential interactions between NSAIDs and other medications exist and should not be taken lightly.

Social factors

Immobility may adversely affect compliance. Older patients will sometimes complain that they are housebound and unable to fill a prescription because of inclement weather or lack of transportation. Patients may also become housebound by habit; as a result, they are susceptible to boredom and mental and physical deterioration. A study by a team of Australian investigators found that less socially active residents of a retirement village were more likely to take multiple medications.[15] Frequent office visits or follow-up phone calls may be needed to assure the patient's continued cooperation.

Patient preferences

It is important to tailor therapy to the needs of the individual patient. It may be beneficial to experiment with scheduling. Pain and inflammation rise and fall in circadian rhythms; thus, there may be individualized optimal times for drug administration.[4] Timing this schedule with meals may make it difficult to follow such a practice: NSAIDs are best administered with food, but the patient's pain patterns may call for administration at odd hours. Close attention must be paid to any patient complaints, especially gastrointestinal complaints. They may indicate the individual clinical response to the prescribed NSAID, but more importantly, they may signal the onset of life-threatening adverse effects.

Geriatric patients may find the typical NSAID tablet difficult to swallow. Some agents are available in liquid rather than tablet or capsule form. Naproxen and ibuprofen are examples. This simple switch may be a solution to some stubborn compliance problems and may also lessen the chance of the patient's confusing the NSAID with another of his or her regular daily medications.

Cost

Because of the expense involved in developing and marketing new NSAIDs, the ultimate cost to the patient can be quite high. Cost may come into play when choosing between two compounds with similar risk profiles.[3] The potential savings effected in selecting one NSAID over another can be significant—up to a factor of 4.[3] A 1-month supply of naproxen or piroxicam costs the patient approximately $70. Generic drugs may offer an alternative, although few NSAIDs are currently available generically.[8]

Table 2
Chemical Classes of Nonsteroidal Anti-inflammatory Drugs

- **Propionic acids**
  Oxaprozin (Daypro)
  Ibuprofen (Motrin)
  Naproxen (Naprosyn)
  Fenoprofen (Nalfon)
  Ketoprofen (Orudis)
  Flurbiprofen (Ansaid)
- **Carboxylic acids**
  Acetylated
  —Aspirin (Zorprin)
  Nonacetylated
  —Diflunisal (Dolobid)
  —Salsalate (Disalcid)
- **Acetic acids**
  Diclofenac (Votaren, Cataflam)
  Indomethacin (Indocin)
  Tomentin (Tolectin)
  Sulindac (Clinoril)
- **Fenamic acids**
  Mefenamic acid (Ponstel)
  Meclofenamic acid (Meclomen)
- **Enolic acids**
  Phenylbutazone (Butazolidin)
  Piroxicam (Feldene)
- **Pyranocarboxylic acid**
  Etodolac (Lodine)
- **Naphthylalanone**
  Nabumetone (Relafen)

Samples should be used at the onset of therapy whenever possible. This practice also familiarizes patients with the color and shape of their new "pill." In addition, sampling avoids an unnecessary expense to the patient should the particular NSAID selected be ineffective or not tolerated.

Comment

The chance of a musculoskeletal disorder developing increases dramatically after the age of 65 years, especially for women. Despite their potential risks, NSAIDs are effective agents in the relief of pain as well as the improvement of joint mobility and the subsequent level of functioning. The effectiveness of NSAID therapy can be seriously hampered by poor compliance and side effects. Older patients are less likely to follow prescribed dosing regimens than are younger patients. Geriatric patients require special physician attention and consideration in order to ensure that NSAID therapy will be both safe and effective.

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