PAIN

(Review article for physicians)

Method of Alexander Mauskop, MD
New York Headache Center, New York, NY.

From Connâs Current Therapy, 1996

PHARMACOTHERAPY

Major advances are being made in the development of new drugs for pain and several are approved by the FDA each year. Pharmacological management remains the mainstay of treatment for many pain syndromes. The three primary groups of drugs used in pain management are non-steroidal anti-inflammatory drugs or NSAIDs, opioids and adjuvant medications.

NSAIDs

Many patients, before seeking medical care, try over-the-counter NSAIDs such as aspirin, ibuprofen (Advil, Motrin), or ketoprofen (Orudis). The physician must establish that the dosage and the frequency of self-administration was sufficient before giving up on this group of medications. Failure of one NSAID to relieve pain does not mean that another one will not be effective. Side effects can also be idiosyncratic. For example, naproxen (Naprosyn) and indomethacin (Indocin) can produce GI side effects in a particular patient while naproxen sodium (Anaprox) and diclofenac (Voltaren) do not.

NSAIDs can be surprisingly effective in the relief of pain from metastatic bone disease. Opioids and NSAIDs have a different mechanism of action and together can have a synergistic effect. This combination may reduce the dose requirement of an opioid with a concomitant reduction in side effects. Longer acting NSAIDs, such as naproxen (Naprelan), piroxicam (Feldene), given at 20 mg once a day or diflunisal (Dolobid), given at 500 mg twice a day, choline magnesium trisalicylate (Trilisate) given at 1500 mg twice a day, nabumetone (Relafen) given at 1000 mg once a day and sustained release indomethacin (Indocin SR), given at 75 mg once a day, are preferred in patients with continuous pain. Short-acting NSAIDs include ibuprofen (Motrin, Advil), given at 400-600 mg every 4 hours, aspirin, given at 650-1000 mg every 3-4 hours and ketoprofen (Orudis), given at 50 mg four times a day. Ketorolac (Toradol) is the only NSAID that is available in a parenteral form. The efficacy of a 30 mg intramuscular injection is comparable to an injection of 10 mg of morphine. Ketorolac (60 mg IM) has replaced dihydroergotamine (DHE-45) as the author's second-line drug after sumatriptan (Imitrex) for office management of an acute migraine attack. The author sometimes injects ketorolac in the office to relieve acute low back or other pains.

Opioids

Important characteristics of opioid drugs and their relative potencies are shown in the Table. Unlike NSAIDs, opioid drugs do not have a ceiling effect. This means that, with the development of tolerance, the dose of an opioid can be escalated indefinitely in order to regain pain relief. Usually, it is the development of side effects that limits escalation, although some patients can tolerate an equivalent of up to several grams of morphine a day given parenterally. With a gradual escalation of the dose, these patients can remain functional as they develop tolerance not only to pain relief, but also to side effects. The development of tolerance to an opioid is usually manifested by a shorter duration of action. Because cross tolerance between different opioids is incomplete, switching to a different opioid may forestall escalation of the dose. Using combinations of NSAIDs and adjuvant analgesics with opioids is another useful approach. Development of tolerance and physical dependence is often mistakenly equated with addiction. In a tolerant patient receiving a high dose of an opioid drug, symptoms of withdrawal can appear within a few hours of the last dose. Addiction, on the other hand, is characterized by craving for the drug, taking the drug despite it's harmful effects and not following a physician's directions regarding usage.

Both physicians and patients often have a fear of opioids because of their potential for addiction. A survey of 10,000 patients in burn units across the country looked at patients receiving large doses of opioid drugs on a daily basis for periods of up to several months. With the exception of patients with a history of addiction not a single patient became addicted. Sometimes the use of an opioid in a cancer patient is equated with imminent death. The author always brings up this topic as many patients do not verbalize their fears and, if not reassured, are reluctant to take sufficient amounts, if any, of the drug. Another obstacle to the proper use of opioids is an exaggerated concern about respiratory and central nervous system (CNS) depression. Tolerance to these side effects of opioids develops quickly. Patients do not become oversedated or stop breathing while in pain. When a patient on a steady dose of an opioid suddenly becomes drowsy or develops respiratory depression, the most likely cause is a new systemic problem, such as an infection or liver or kidney failure. When pain can be controlled only with some degree of sedation, a stimulant, such as dextroamphetamine (Dexedrine) given at 5 mg twice a day, may not only improve the alertness but provide additional analgesia as well. Dextroamphetamine and other stimulants have mild analgesic properties synergistic with opioid analgesia. The major side effect of opioids that must be anticipated is constipation. Senna concentrate (Senokot) is an anecdotal favorite to combat this problem. Transdermal fentanyl (Duragesic) tends to produce less constipation than do oral opioids.

Meperidine (Demerol) is a popular drug, but it is the only opioid that should not

be used with frequency for more than a few days. Meperidine is metabolized into normeperidine which is a central nervous system stimulant. With chronic administration, meperidine can cause irritability, tremor, and generalized seizures.

Until recently the preferred route of administration of medications has been oral. With the introduction of transdermal fentanyl (Duragesic) the author has found that many patients do better on the fentanyl patch. This product provides a steady level of an opioid drug with practical and psychological benefits. Each patch lasts for about 3 days and comes in four strengths (25, 50, 75 and 100 mcg per hour). Because of the long half-life of the drug the process of determining the optimal dose of the patch may take up to a few weeks. While this adjustment is being made patients should be given a short-acting opioid such as oxycodone (Percocet, Percodan, Tylox, Roxicet), morphine sulfate (Roxanol, MSIR) or hydromorphone (Dilaudid) as a rescue medication for breakthrough pain. This also applies to the titration phase of other long-acting oral opioids, including sustained release morphine (MS Contin, Oramorph SR), sustained release oxycodone (Oxycontin), methadone (Dolophine) and levorphanol (Levo-Dromoran). Methadone is an excellent analgesic with good absorption and, in the author's experience, fewer side effects than other opioids. It is also one of the most inexpensive opioids, although it can be difficult to obtain from some pharmacies.

Rectal suppositories of morphine (Roxanol, RMS), hydromorphone (Dilaudid) and oxymorphone (Numorphan) are useful for patients who cannot take oral preparations. The rectal route is not practical for long-term management and when high doses are needed.

Intranasal administration of butorphanol (Stadol NS) offers a rapid onset of action. The limitation of this drug in current formulation is that each spray contains a dose that is excessive for many patients. This results in a high incidence of CNS side effects. Reformulation at a lower dose may improve the utility of this drug. Butorphanol is a partial agonist-antagonist drug with a lower potential for addiction. It should not be given to patients who are maintained on opioids that are pure agonists (see Table) because the antagonist properties can induce a withdrawal reaction. Patients on chronic opioid maintenance become very sensitive to all opioid antagonists. Should a need arise to reverse the effect of an opioid in such a patient, naloxone (Narcan) must be diluted with saline and infused very gradually.

When a patient with continuous pain cannot take oral medications, subcutaneous (SC) infusion of opioids is an alternative to the transdermal route that has many advantages over the intravenous infusion. The patch should be tried first, but when it is ineffective at a high dose (e.g. 2 of 100 mcg Duragesic patches) or causes side effects SC infusion is the method of choice. SC infusion is administered using a programmable, portable pump that can be

filled with a solution of any opioid, including morphine, hydromorphone, methadone and levorphanol. The pump is connected to a 25 gauge "butterfly" needle that can be inserted subcutaneously by the patient or a family member. An intravenous infusion of an opioid may be necessary only if a patient requires a very large volume of an opioid or if other routes are not tolerated.

The use of opioid analgesics has been mostly limited to cancer patients. Their prolonged use in non-cancer pain patients remains controversial. Many anecdotal reports and the author's personal experience suggest that under strict supervision selected non-cancer pain patients can derive great benefits from chronic opioid therapy. Such patients are usually those who do not develop significant tolerance and remain on a steady dose for long periods of time with few side effects. The author obtains a verbal informed consent from such patients warning them about the risk of addiction, sees them at least once a month and tries to make opioids only a part of the pain management program.

Adjuvant analgesics

This is a very diverse group of medications that were not known to have analgesic properties when they were first introduced. The most useful drugs for chronic pain and headache management are tricyclic antidepressants (TCA).

Among the TCAs, amitriptyline (Elavil) has been studied most extensively but nortriptyline (Pamelor), imipramine (Tofranil), and desipramine (Norpramine) are also effective and may produce fewer anticholinergic side effects. If one TCA is ineffective or produces unacceptable side effects another TCA should be tried.

The starting dose for any TCA are 25 mg in a young or middle-aged patients and 10 mg in elderly or debilitated persons. The average effective dose is 50 to 75 mg taken once a day in the evening. Some patients may require and tolerate antidepressant doses of up to 300 mg a day or more in order to achieve pain or headache relief. Patients must be told that these medications are anti-depressants, but that they are also used for chronic painful conditions, even if there is no associated depression. If patients discover from other sources that they were given an antidepressant drug, they often become angry and non-compliant; they may think that their complaints were interpreted as depressive symptoms and not real pain. Warning patients about possible side effects such as dryness of the mouth, drowsiness, and constipation also improves compliance. Some of the contraindications for the use of TCAs include concomitant use of monoamine oxidase inhibitors, recent myocardial infarction, cardiac arrhythmias, glaucoma and urinary retention. An electrocardiogram should be obtained before the initiation of treatment in all elderly patients.

Other antidepressants including the selective serotonin re-uptake inhibitors (SSRI) fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), as well as non-SSRI antidepressants bupropion (Wellbutrin SR) and nefazodone (Serzone), may have some utility in pain management. No large trials of these drugs have been conducted in pain patients to show any benefits beyond their antidepressant effect. The author frequently starts with these antidepressants before resorting to TCAs because of their favorable side effect profile. SSRIs do not cause weight gain, drowsiness and anticholinergic side effects, all of which can occur with TCAs. Nefazodone (Serzone) and bupropion (Wellbutrin SR) do not cause sexual dysfunction which can occur with SSRI drugs.

Anticonvulsants that are commonly used for pain relief are carbamazepine (Tegretol) and phenytoin (Dilantin). It has been suggested that anticonvulsants are more effective for sharp, lancinating pain, while TCAs are better for burning, dysesthetic pain. Newer anticonvulsants, lamotrigine (Lamictal) and gabapentin (Neurontin), are being studied for their potential analgesic efficacy as well.

Dextromethorphan, which is in wide use as an anti-tussive agent, has been found to have analgesic properties and possibly delays the development of opioid tolerance. This drug produces analgesia through its blocking effect on the N-methyl-D-aspartate (NMDA) receptor. A gradual escalation of the dose up to 60 mg QID or more is often necessary to achieve an analgesic effect.

Hydroxyzine (Vistaril, Atarax) may have some mild analgesic properties, but what makes it a useful adjuvant analgesic is its reduction of anxiety and nausea. Caffeine has been shown to enhance the effect of other analgesics and to have mild analgesic properties of its own. It is useful in a variety of pain syndromes, but it is most commonly used for headaches. Overuse of caffeine in drinks (coffee, tea, colas) and medications (Excedrin, Anacin, Fiorinal, Esgic, Norgesic) can lead to severe withdrawal headaches and other symptoms. As little as 3 cups of coffee a day can induce a withdrawal syndrome.

Corticosteroids can be very effective in relieving pain from various causes. Long-term side effects and loss of efficacy limits their use to treatment of acute pain syndromes, such as spinal cord, a plexus or nerve compression or severe migraine or back pain.

Benzodiazepines usually have little utility in pain management, except for acute pain of muscle spasm, such as in acute low back or neck pain or in a very anxious patient. A short course (up to few weeks) of diazepam (Valium) or clonazepam (Klonopin) in those circumstances carries little risk of addiction and may be of significant help

PSYCHOLOGICAL METHODS

These methods are indispensable in the management of patients with chronic pain. Pain affects all aspects of chronic pain patients' lives and the lives of people who surround them. For this reason, a psychologist is a crucial member of the pain management team. Chronic pain of long duration is very unlikely to respond to a single treatment modality. Patients should not be allowed to pick and chose their treatment. The author explains to such patients that pain control can be achieved only by attacking the problem with several methods at the same time. Psychological methods may include behavior modification, cognitive psychotherapy, biofeedback, and relaxation training. On occasion, in an anxious patient with acute or cancer pain, simple reassurance may reduce the need for opioid analgesics. In some patients music therapy can have beneficial effects.

ANESTHETIC APPROACHES

Muscle spasm is a common primary cause of pain and it often accompanies pain of other types. Trigger point injections are very effective in the management of acute pain due to muscle spasm. These injections can be done using a 1% lidocaine solution and must be combined with active physical therapy (by the word active the author implies an emphasis on strengthening exercises rather than passive modalities, such as heat, ultrasound, massage, etc.).

Nerve blocks can provide temporary relief of pain in patients with local pain. Some physicians use the block to predict possible efficacy of a nerve ablation. Instead of a local anesthetic which tends to have a very brief effect the author usually injects a corticosteroid such as betamethasone (Celestone Soluspan) or methylprednisolone (Depo-Medrol) into an area around the nerve. Although such an injection cannot be considered a nerve block, similar techniques are used for both procedures. Examples of conditions that benefit from corticosteroid injections include carpal tunnel syndrome, meralgia paresthetica, and occipital neuralgia.

Sympathetic block is the most effective procedure for the treatment of reflex sympathetic dystrophy, especially when blocks are combined with vigorous physical therapy and, if necessary, pharmacotherapy and psychological methods. This combined treatment works best if it is started early in the course of the disease.

Epidural and spinal infusions of opioids and local anesthetics are useful in some cancer patients and in a few selected patients with a "failed back syndrome".

NEUROSURGICAL METHODS

In attempting to stop transmission of pain signals up along the nervous

system, neurosurgeons have tried placing lesions anywhere from the peripheral nerves all the way up to the frontal cortex. Nerve section can be effective in patients with meralgia paresthetica, occipital neuralgia and some other focal neuropathic pains. It is not effective, however, in patients with post-herpetic neuralgia. Some patients with trigeminal neuralgia find temporary relief when a nerve leading to the trigger area is sectioned. Dorsal root entry zone (DREZ) lesion can sometimes relieve pain due to brachial plexus avulsion and anesthesia dolorosa. Section of half of the spinal cord (cordotomy) is very effective in patients with cancer who have unilateral pain below the waist. Bilateral cordotomy usually leads to loss of sphincter control and should be reserved for cancer patients who have already lost such control. Hypophysectomy should be considered in women with hormonal cancers (breast or ovarian) whose pain is resistant to other modalities.

PHYSICAL METHODS

Physical therapy is the main treatment modality for most patients with low back and neck pain. It is also essential in the management of complex regional pain syndrome (reflex sympathetic dystrophy). Patients with almost any pain syndrome benefit from regular exercise. Improved cardiovascular and pulmonary function from aerobic exercise is of significant benefit in itself, but it also provides important psychological benefits. Patients feel that they are regaining some control over their bodies and feel less helpless and hopeless. Regular exercise helps to alleviate stress, which is a major contributing factor in chronic headaches, back pain, and other pain syndromes.

Other physical methods include transcutaneous electrical nerve stimulation (TENS) and acupuncture. Neither method has been scientifically proved to be effective; however, a large body of anecdotal evidence indicates that they can be very helpful in some patients. Results of experiments detailing opioid and non-opioid mechanisms of acupuncture analgesia in animals, as well as the successful use of acupuncture in veterinary medicine suggest that the effect of acupuncture is superior to that of placebo. The author usually uses acupuncture in the elderly or other patients, who do not tolerate any medications, and patients who have tried a variety of therapies without relief. In patients with chronic pain, acupuncture should be used as a part of multidisciplinary approach.

Chiropractic, osteopathic and other methods of manipulation are in wide use for a variety of painful conditions. With the exception of vigorous neck manipulation these methods are generally safe. These therapies can provide lasting relief for some acute pain syndromes, such as low back pain, especially when they are used together with active physical therapy. Prolonged use of these methods should be avoided because they divert patients from obtaining more effective treatments and because of the cost.