A Rational Approach to Cancer Pain Management

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The therapeutic modalities available in oncology are constantly changing. Mitoxantrone, a new antineoplastic agent, is a recently marketed cousin of the anthracycline antibiotics (eg, Adriamycin).[1] The biological response modifiers—interferon, interleukin-2, granulocyte-macrophage colony-stimulating factor—have already had a huge impact upon cancer patients and their treatment options. For the treatment of infection in neutropenic patients, we are always being armed with a new weapon—first the third-generation cephalosporins and fourth-generation penicillins, then imipenem/cilastatin, and now aztreonam. The new fluoroquinolone antibiotics have tremendous potential. Antiemetic therapy has seen the emergence of high-dose metoclopramide for cisplatin, and a deep new appreciation for yet another use of corticosteroids; the new intravenous serotonin blockers are threatening to further revolutionize our approach to nausea and vomiting.[2–4] For the treatment of cancer pain—perhaps the most devastating aspect of the disease—patient-controlled analgesia and epidural catheters have given us new versatility.[5,6] Buprenorphine is a relatively new parenteral mixed agonist-antagonist opioid with some attractive features.[7] An hour spent on rounds on an oncology ward will convince most clinicians that further improvements in pain management would be most welcome. Certainly we need more new drugs—or do we?

The article by Brooks et al in this issue of the *Journal* is timely; it is also long overdue. Brooks et al provide us with an orderly approach to the oral management of cancer pain using a drug that has been around for centuries: morphine sulfate. The standard of analgesic reference has always been 10 mg of intramuscular morphine, and for good reason. Morphine has well-defined opioid receptor pharmacology and clearly described pharmacokinetics, including an attractive half-life of three to four hours.[8] Its side effects, although they demand respect, are predictable and easily dealt with. It is an incredibly versatile agent. Morphine may be administered orally, intravenously (by bolus and continuous infusion), intramuscularly, epidurally, intrathecally, intraventricularly, subcutaneously, sublingually, and rectally. The pharmaceutical companies have cooperated and are to be commended for the availability of the many different dosage forms.

Much of the debate in the approach to oral pain management in cancer still involves the usefulness of methadone, an admittedly effective drug with a dismally long half-life. If a clinician wishes to use oral methadone, he must respect its pharmacokinetics.[9] Analgesia after a dose of oral methadone lasts six to eight hours, but the drug accumulates over five to seven days (because of its 24-hour half-life); side effects (such as sedation) will intensify as the agent accumulates. Accumulation is even more exaggerated in patients with significant hepatic dysfunction. To respect the pharmacokinetics of methadone means to choose a dose and stick with the dose until steady state levels are somewhat achieved, four or five days later, before altering that dose. Otherwise one fights the notorious battle with methadone of endlessly tinkering with the dose to combat either inadequate analgesia or excessive sedation. In today's hectic world of medicine, it is simpler and also intellectually satisfying to work with a drug that has a brisk half-life and whose dose may be altered with confidence on a daily basis, depending on the day-to-day status of the patient. Such a drug is morphine.

If methadone ever had an advantage over morphine for cancer pain management, it might have been the ability to dose methadone every six or eight hours. Before the advent of sustained-release morphine, oral morphine was clearly an inconvenient four-hour analgesic. Brooks et al provide us with a logical framework for eventually dosing our patients on sustained-release morphine every eight or 12 hours, in short, the compliance advantages of methadone with the favorable pharmacokinetics of morphine in one tablet. The idea is elegant in its simplicity.

Brooks et al maintain that oral morphine can replace other opioid analgesics in a patient's regimen. Why bother? Side-effect profiles provide compelling reasons. Meperidine is a horrendous choice for cancer pain management because of its centrally toxic demethylated metabolite, normeperidine. Normeperidine is renally cleared and has a prolonged half-life. While low levels may be responsible for the well-known meperidine euphoria that patients ex-

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perience, meperidine-induced seizures are commonly seen with sizable doses of the drug and are frequently difficult to control.[10] Codeine is often an effective analgesic, but codeine and nausea are synonymous for many cancer patients. Nalorphine-like mixed agonist-antagonists such as pentazocine are associated with significant psychotomimetic effects and may cause withdrawal symptoms in opioid-dependent patients.[7] Methadone has the previously mentioned problem of toxic accumulation.

There are yet other reasons. Hydromorphone is often a useful alternative opioid because it seems to have the least side effects for a given degree of analgesia. But hydromorphone suffers from the need for frequent dosing, thanks to a two- to three-hour half-life and the conspicuous absence of a sustained-release form. Oxycodone is just not potent enough for successful treatment of severe pain. Propoxyphene often borders on the ineffective, and buprenorphine, the new morphine-like mixed agonist-antagonist, is available only in a parenteral form. Once again, we are left with morphine.

Brooks et al suggest the use of adjuvants to minimize opioid dosage and hence mitigate troublesome side effects. We would do well to apply this concept more often. For patients with painful bony metastases who have adequate platelet function and are not at particular risk for gastritis, nonsteroidal anti-inflammatory agents such as ibuprofen are quite effective in combination with opioids.[11] Low doses of tricyclic antidepressants such as doxepin, amitriptyline, and imipramine can be very effective adjuvants in patients with a wide variety of chronic pain syndromes, as well as in depressed patients and patients with pain-related sleep disorders.[12] Trigeminal neuralgia responds to anticonvulsants such as carbamazepine and phenytoin.[13] Dexamethasone is often effective for pain that is due to tumor infiltration of neural structures, such as the brachial plexus.[13] Dextroamphetamine and methylphenidate provide increased analgesia in combination with opioids and serve to reduce morning sedation.[14] Finally, antihistamines such as hydroxyzine probably do not augment analgesia, but they are weakly antiemetic and may provide useful anxiolysis.[15] A greater awareness of all of the above options will surely come about through future controlled trials.

We must always remember the basic principle of morphine use, or any opioid, as outlined by Brooks et al. There is no firm ceiling dose of opioid. Titration upward of the dose should occur until analgesia is accomplished or until some unacceptable side effect intervenes. The goal of completely acceptable analgesia is a very realistic one and should be pursued by everyone connected with cancer pain management. Moreover, we can be as organized with our approach to pain as we are with our approach to infection, nausea, nutrition, or the malignancy itself. The concepts outlined in this paper are a definite step in the right direction.

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