Recent Advances in Clinical Use of Opioids

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Introduction
Opioids likely are the oldest class of drugs still in regular therapeutic use. This use certainly is not limited to the treatment of pain. They are used to treat anxiety, dyspnea, diarrhea, and even pulmonary edema. Despite their venerable emeritus status in our armamentarium, opioids remain a subject of intense research in basic science laboratories and clinics. The pharmaceutical industry also has not been blind to the importance of opioids. Industry is now launching, or will soon launch, the sale of several new opioid analgesics.

It was only 1 year ago in this very journal that I reviewed recent developments in opioids [1•]. However, the ongoing developments in opioid therapy, especially in clinical trials, justify another review. This review surveys recent developments in these clinical trials and provides an overview of what may be expected in the near future for opioid management of pain.

The Need for Several Opioids
The clinical justification for a multitude of opioids is not self-evident. The heuristic model of opioid action, which compares it with a key fitting into a lock, is an apt one. Opioids exert their pharmacologic action by binding to specific receptors on cell surfaces, especially on the surfaces of neurons. Once the receptor is activated, it should make little difference what the structure of the activating molecule is. By comparison, whether a key is made of iron, bronze, or aluminum should make little difference in the matter of opening a door, so long as the key fits properly into the lock. However, the clinical experience with opioids belies this easy analogy. There are patients who respond quite well to one opioid, but not at all to another. Patients exhibit limited cross-tolerance when one opioid is substituted for another.

The explanation for these observations is not to be found merely in vagaries of pharmacokinetics, clearance mechanisms, or lipid solubility. There is a pharmacodynamic distinction among opioids that varies by drug and by patient.

Only one gene encoding the µ opioid peptide receptor has been discovered. However, this one gene may be expressed in a multitude of splice variants. The variable receptors, in turn, may vary in their ability to bind different opioid analgesic drugs. This variable responsiveness to different opioid analgesic drugs is a heritable condition [2••]. For example, there are strains of mice that exhibit no analgesic response to morphine, but respond appropriately to fentanyl [3]. Splice variants of µ opioid peptide receptors already have been discovered in humans and it is reasonable to assume that these variants may play a role in the variable response to administered opioid analgesics routinely seen in clinical practice.

Thus, the availability of a wider variety of opioid analgesics is to be welcomed. It will allow clinicians to match the drug to the patient better than what can be done now. The one-size-fits-all approach clearly is inadequate.

Another implication of the existence of splice variants of µ opioid peptide receptors is the possibility of clinical benefit from coadministration of two opioid analgesics. Of course, a mere additive benefit would be of little importance. Additive benefit could be achieved as readily simply by increasing the dose of just one of the opioid analgesic drugs. However, if the drugs are binding to somewhat different receptors, there is the possibility of synergistic effect. This would be a boon, unless the toxicity of the combination also were synergistic. Bolan et al. [4] found that methadone exerted a synergistic analgesic action when combined with morphine. However, they observed only additive effects from combining methadone with oxymorphone, oxycodone, fentanyl, alfentany, or meperidine. They also noted that the methadone/morphine combination did not exhibit syn-
Various New Products

Overview

There are no truly new opioid analgesic molecules expected to receive approval from the US Food and Drug Administration (FDA) this year. However, a number of older drugs have been reformulated in different delivery mechanisms. This increases the options available to the clinician. If a drug previously was simply unavailable in a sustained-release form, its new availability in sustained-release form is as good for the patient as if the drug were a newly discovered entity.

Hydromorphone

Hydromorphone is one example of old wine in a new flask. The entity has been available in oral, rectal, and parenteral formulations for decades. However, Purdue Pharma is expected to market Palladone (hydromorphone controlled-release, Purdue Pharma L.P., Stamford, CT), a sustained-release form of the drug, in the near future. A number of studies have described the activity of sustained-release hydromorphone.

Angst et al. [5] studied the pharmacokinetics and pharmacodynamics of sustained-release hydromorphone in healthy volunteers subjected to experimental pain and compared that with the results seen with the immediate-release formulation. They found that the hydromorphone plasma concentration peaked significantly later, but was maintained significantly longer (at more than 50% of peak concentration) after sustained-release than after immediate-release hydromorphone. Similarly, sustained-release hydromorphone produced analgesic effects that peaked significantly later, but were maintained significantly longer (at more than 50% of peak analgesic effect). They noted that the analgesic action of the sustained-release formulation provided analgesia to experimental pain beyond 24 hours of its administration.

Drover et al. [6] also studied the effect of sustained-release hydromorphone on healthy volunteers. However, the focus of their study was not on pharmacodynamics, but only pharmacokinetics. Not surprisingly, they found significantly less plasma concentration fluctuation from the sustained-release formulation compared with that after administration of the immediate-release formulation. They noted that the sustained-release formulation produced continued release of medication over 24 hours, which should allow for once-daily oral dosing.

Although studies on healthy volunteers provide useful information regarding pharmacokinetics, only studies on patients in pain will reveal how useful an analgesic is. Palangio et al. [7] studied the effect of sustained-release hydromorphone on a population of more than 400 patients, most of whom had chronic non-malignant pain. Their open-label study used an initial conversion ratio of 5 mg of oral morphine or its equivalent of 1 mg of oral hydromorphone. Most of the patients were able to arrive at their optimal dose of sustained-release hydromorphone with two or fewer titration steps. This clinical trial did not use an intermediate step of immediate-release hydromorphone to find the ideal dose of that drug. Rather, the patients went directly from their former opioid therapy to the sustained-release hydromorphone. Most patients reported better pain control than they had formerly and the side effects were typical of those associated with opioid therapy. However, the authors noted that their study design does not allow conclusions regarding comparative efficacy between sustained-release hydromorphone and other opioid therapies.

Whereas most of the patients in the study by Palangio et al. [7] had non-malignant pain, those studied by Bruera et al. [8] had cancer pain. After being stabilized on an initial opioid analgesic, the patients were switched to sustained-release hydromorphone and the dose was titrated to maximum benefit. In a double-blind fashion, the patients then continued on the sustained-release hydromorphone or received multiple daily doses (in equal overall amount) of immediate-release hydromorphone. After 5 days, the patients crossed over to the different form of hydromorphone. There was no significant difference between these two formulations in pain relief or side effects. Of course, in clinical practice, the sustained-release formulation of hydromorphone would be more convenient than the multiple dosings required by the immediate-release formulation.

Oxymorphone

Oxymorphone is another opioid analgesic that has been available, but not as an oral formulation. Endo Pharmaceuticals (Chadds Ford, PA), in association with Penwest Pharmaceuticals (Danbury, CT), has developed a sustained-release formulation of this agent and their new drug application (NDA) filing was accepted by the FDA in early 2003 [9]. The product is being developed for twice-daily dosing in patients with moderate to severe pain. An NDA filing for an oral formulation of oxymorphone immediate-release also was accepted by the FDA. These oxymorphone products should provide welcome options in the oral therapy of pain.

Avinza

Quite unlike oxymorphone, morphine has long been available in a large number of formulations. It is now available in one more. Avinza (morphine sulfate extended-release capsules, Ligand Pharmaceuticals, San Diego, CA) is a once-daily morphine sulfate controlled-release formulation developed by Elan (San Diego, CA) and Ligand [10]. It comes as a capsule containing multiple tiny beads.