

Don't Let Fear of Opioid Abuse Inhibit Therapies

BY KERRI WACHTER
Senior Writer

BETHESDA, MD. — Physicians can help minimize the potential for abuse of opioid pain medications by considering the agents' delivery route, bioavailability, and pharmacokinetics, said Dr. Pamela P. Palmer, director of PainCARE (Center for Advanced Research and Education) at the University of California, San Francisco, at a meeting of the National Institute on Drug Abuse.

"One thing we don't ever want to do is inhibit good pain therapies because we're afraid of abuse and diversion," said Dr. Palmer, who is also chief medical officer of AcclRx Pharmaceuticals Inc., which is developing delivery methods to limit opioid abuse.

Dr. Palmer recommends matching opioid half-life with the indication. "You want short-acting drugs for short-acting problems and long-acting drugs for long-acting problems," she said.

The same goes for route of delivery: Match the route with indication. For example, transdermal patches may be less than ideal for acute situations but work well in the chronic setting.

When choosing the optimal route, avoid options with poor bioavailability. Low bioavailability means that higher doses are needed to get the required effect. This excess loading contributes to the amount of drug available for abuse and diversion. For example, the bioavailability of oral oxycodone is 10%. Ten times the intravenous dose would be required to achieve the same response orally.

Extended-release formulations with low bioavailability pose a particular risk for diversion and abuse. For example, a drug that is 10% bioavailable would require 10 times the intravenous amount to achieve the same response. To use a short-acting compound for long-acting pain with twice-daily dosing, the amount of drug needed goes up again, meaning that a lot of drug is now available for diversion and abuse.

In contrast, methadone is rarely abused for practical reasons. The drug is 100% bioavailable. The same amount of drug is available regardless of how it's administered. In addition, methadone is long lasting, based on the nature of the molecule, so an extended-release formulation isn't necessary. If you're suspicious about a patient possibly diverting or abusing opioids, "this is a great drug to start with."

Transdermal delivery of opioids involves a delay in onset of action—about 4 hours. For this reason, Dr. Palmer thinks these drugs are not the best options for breakthrough pain. In the setting of outpatient cancer breakthrough pain, it's important to have fast-, short-acting compounds. This avoids layering on excess opioids when breakthrough pain resolves after a short time.

There are a number of new and upcoming ways to avoid the potential for abuse. One problem is that opioid drugs can be crushed or rapidly extracted with alcohol. The SABER (sucrose acetate isobutyrate extended release) technology overcomes this problem because the viscous gel locks the drug into the matrix, despite attempts to crush or melt it, or extract it with alcohol.

Another option is to add antagonists, such as naloxone and naltrexone. Naloxone has a bioavailability of 3% when taken orally, so when a patient takes a drug like Suboxone (buprenorphine and naloxone in a 4:1 ratio) sublingually, "they're not having any inhibition of the mu-opioid receptor due to the naloxone." But if they attempted to crush and inject the drug, there would be 100% bioavailability of naloxone, and it would inhibit the action of buprenorphine, said Dr. Palmer. The drug is made by Reckitt Benckiser Pharmaceuticals Inc.

A similar drug, Oxytrex (oxycodone and naltrexone), is being developed by Pain Therapeutics Inc. and currently is in phase III trials. "What they're finding in their studies is that there may be less euphoria and less physical withdrawal related to this compound, compared with just the native oxycodone," said Dr. Palmer.

In 2006, the FDA approved Ionsys (fentanyl iontophoretic transdermal system). This patient-activated analgesic system is indicated for the short-term management of acute postoperative pain in adult patients requiring opioid analgesia during hospitalization. The system (made by Alza Corp.) delivers a preprogrammed, 40-mcg dose of fentanyl through the skin over a 10-minute period. The drug is 100% bioavailable, said Dr. Palmer.

AcclRx is developing a sublingual sufentanil "nanotab"—six times smaller than a nitroglycerin pill—with 90% bioavailabil-

Bioavailability of Pain Meds

Drug	Bioavailability
Fentanyl patch	30%-70%
Fentanyl transmucosal	50%-65%
Oral hydromorphone	30%-35%
Oral morphine	30%
Oral oxycodone	60%-80%
Oral oxycodone	10%

Source: Dr. Palmer

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ity. Abusers "could crush this if they wanted to, but it's along the order of methadone: They're not going to get any advantage by crushing it and shooting up," said Dr. Palmer.

Another problem is the tracking of opioids. "I can track a pair of socks through FedEx or UPS from New Jersey to California, yet when I write an OxyContin prescription, I have absolutely no idea how it's used," said Dr. Palmer. With the technology that's available to track those socks, why isn't there a better way to track the use of prescription opioids, she queried.

Currently, Purdue Pharma L.P. uses radio-frequency identification (RFID) tags on bottles of OxyContin. However, this technology tracks the drugs from the manufacturer to the pharmacy only and does not help a physician to monitor patient use.

AcclRx is planning to use computerized dispensers for nanotab products that will allow physicians to download a patient's dosing history. Such technology also could be helpful in assuring that patients aren't confused by dosing regimens. ■

Isometric Exercise May Benefit Patients With Chronic Pain

BY KERRI WACHTER
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WASHINGTON — Low-intensity isometric exercise appears to significantly ease the perception of pain in healthy young adults, suggesting that such maneuvers could be a pain management tool for older adults with chronic pain conditions but limited mobility, according to research presented at the annual meeting of the American Pain Society.

In the study, 22 college-age adults performed isometric contractions of the left elbow flexor muscle at an intensity equal to a quarter of their maximal voluntary contraction held until task failure. Following the exercises, the duration it took for patients to first feel experimental pain, or the pain threshold, increased by 50%, compared with baseline, reported Marie Hoeger Bement, Ph.D., professor of physical therapy at Marquette University in Milwaukee.

These findings could have important implications for patients with chronic pain conditions. "Isometric contractions are very easy to prescribe and individualize," said Dr. Bement. These exercises are especially useful in patients with limited mobility or a fear of falling. "Almost anybody can do it."

To measure the participants' baseline pain threshold, a weighted blade was placed for 2 minutes on the right index finger of the 11 men and 11 women. The students held a timer in their left hands and were instructed to trig-

ger the timer when they first felt pain. The students also were asked to rate their pain on a 0-10 point scale every 20 seconds during the 2-minute test.

Each student participated in four sessions. For the first session, students performed three maximal voluntary contractions (2 seconds in duration). The next three sessions were randomized.

Patients could be asked to perform a contraction at 25% maximal voluntary contraction to failure (8 minutes on average), at 25% maximal voluntary contraction for 2 minutes, or at 80% maximal voluntary contraction to failure (40 seconds on average). A force transducer measured the force of the contractions. Intensity was based on a percentage of the maximal contraction.

During the session of three maximal voluntary contractions, there was a statistically significant increase in pain threshold over baseline, a finding that Dr. Bement said was "very surprising." She added, "I'm amazed at what potential exercise has in managing some of chronic pain conditions."

Pain ratings at 40, 60, and 80 seconds also were significantly decreased. The effect on pain rating appears to be short lived, however, as pain ratings returned to baseline levels by 2 minutes.

When students performed at 80% maximal voluntary contraction, there was no change in the pain threshold; however, there were improvements in pain ratings at 40 and 60 seconds. When students performed at 25% max-

imal voluntary contraction for 2 minutes, there were no changes in either the pain threshold or the pain ratings.

When students performed at 25% maximal voluntary contraction to failure, there was a roughly 50% increase in pain threshold over baseline. Likewise, pain ratings were decreased at all time points between 40 and 120 seconds.

During the low-intensity, long-duration session, women reported greater pain ratings than did men, both before and after contractions. Women also reported greater increases in pain than did men during the 2 minutes measured. "What's really exciting is that women have a tendency to report greater decreases in pain than men after that low-intensity, long-duration contraction." So they're experiencing a greater analgesic effect than are men, Dr. Bement said.

To assess whether the sex difference in pain perception was because of hormonal fluctuations in the women, the researchers recruited 20 healthy, college-age women to perform the low-intensity, long-duration contraction (25% maximal voluntary contraction until failure). The women were tested during the midfollicular phase (5-8 days past menses) and the midluteal phase (6-8 days past ovulation). Ovulation was determined using an ovulation test kit.

Baseline pain threshold did not vary with hormone phase. The pain threshold increased with contraction for both menstrual phases, similar to the increases seen in the previous study. Likewise, phase made no difference in pain ratings. Similar to the first study, the women reported decreased pain from 40-100 seconds with exercise, regardless of phase. ■

'Isometric contractions are very easy to prescribe and individualize.' These exercises are useful in patients with limited mobility or a fear of falling.