Unapproved Narcotic Gets Reprieve From FDA

BY SHERRY BOSCHERT

The Food and Drug Administration has backed off from a warning letter it sent to several manufacturers and decided to allow an unapproved version of high-concentrate morphine sulfate oral solution to remain on the market.

Objections from pain specialists, hospice workers, and patients convinced the FDA that there is no good alternative for some patients who need the immediate-release morphine sulfate oral concentrate solution 20 mg/mL for pain control, Dr. Douglas Throckmorton of the FDA's Center for Drug Evaluation and Research said at a press briefing.

The decision will benefit patients at the end of their lives who cannot easily be administered opiates intravenously or through other routes and cannot swallow well. They may need a high morphine dose—several hundred milligrams—and an approved, less-concentrated morphine sulfate elixir would require a large volume of liquid, putting them at risk of aspirating the liquid.

As part of an ongoing crackdown on unapproved drugs in the United States, the FDA on March 30 had written to nine companies warning them to stop making and marketing 14 unapproved narcotic products, believing that acceptable alternatives were available.

The March 30 action alarmed members of four organizations in the Palliative Care Coalition, whose leaders communicate regularly and who quickly drafted a letter apprising the FDA of the medical necessity for the concentrated morphine elixir.

In addition to use in patients near the end of life, the elixir is used to manage pain in "patients who are not dying but [are] going through very traumatic treatment for head and neck cancer, which is likely to be curative but very difficult to get through," Dr. Diane E. Meier said in an interview. She is director of the Center to Advance Palliative Care at Mount Sinai School of Medicine, New York. The Palliative Care Coalition consists of her organization and the American Academy of Hospice and Palliative Medicine, the Hospice and Palliative Nurses Association, and the National Hospice and Palliative Care Organization.

In response to the outcry, the FDA sent follow-up letters on April 9 to six companies that offer the concentrated morphine sulfate elixir, saying they could continue to market the drug formulation. This should especially help some patients in hospitals and hospices, Dr. Throckmorton acknowledged.

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DR. MEIER

"Both those populations sometimes experience severe pain at the end of life and want to be able to be managed at their homes whenever possible. The use of this elixir enables that," he said. "That's an important part of the decision that we made today."

The reversal surprised and delighted observers. "I don't think we expected a response" from the FDA to the coalition's letter, Dr. Meier said, "so to get one was really gratifying and made us very optimistic that this will be the beginning of an effective professional dialogue."

Mike Cohen, president of the nonprofit Institute for Safe Medication Practices in Horsham, Pa., commented on Twitter.com: "First time in recent history I can remember FDA reversing a warning letter so quickly!"

The concentrated morphine elixir products were marketed before the 1938 Federal Food, Drug, and Cosmetic Act regulations took effect, and were allowed on the market without formal approval under a grandfather clause. The FDA today believes few drugs are entitled to grandfather status, Mr. Cohen wrote in the institute's April 9 newsletter.

The FDA is willing to fast-track an approval application from any company for the concentrated morphine sulfate elixir, Dr. Throckmorton said. If one gets approved, any companies making unapproved versions will have 180 days to cease manufacturing and marketing their formulations. Until one is approved, however, they can continue to supply the product.

The other unapproved drugs that were targeted in the original warning on March 30 must still be taken off the market within 90 days. These include immediate-release hydromorphone and oxycodone tablets. Failure to comply could result in seizure of these drugs.

Dr. Meier says the coalition remains concerned about those drugs being taken off the market, too. "There is a nationwide shortage of opioids," she said. "In New York City you can't find many of these drugs, even before this shutdown has taken place. My colleagues report this to be true across the country."

Dr. Meier and others planned to participate in an invitation-only meeting with FDA officials on May 4 to discuss Risk Evaluation and Mitigation Strategies (REMS) for drugs including opioids. Coalition members are concerned that REMS requirements could further decrease patient access to pain medications, but are hoping that the flexibility shown by the FDA regarding the morphine elixir bode well for future talks.

"I found the responsiveness and timeliness of the FDA to be really wonderful. It reinforced the FDA's obligation to not only reduce harm but [also] to ensure access to beneficial medications," Dr. Meier said.

The companies that received the April 9 letter allowing them to continue offering morphine sulfate oral solution 20 mg/mL are Lannett Co., Lehigh Valley Technologies, Mallinckrodt Inc. Pharmaceuticals Group, Xanodyne Pharmaceuticals Inc., Boehringer Ingelheim Roxane Inc., and Cody Laboratories Inc. ■

Palliative Oxygen May Not Be Worth the Additional Cost

BY PATRICE WENDLING

AUSTIN, TEX. — Palliative oxygen was no better than air delivered by nasal cannulae for relieving dyspnea or improving quality of life in a study of 239 non- or mildly hypoxemic patients with terminal illness.

During the first 24 hours, patients in the O_2 Breathe Trial had an improvement of about 10% in dyspnea symptoms with either treatment, or 1 point on a 10-point self-reported scale. The results were sustained over the 7-day study period, lead investigator Dr. Amy Abernethy and her associates reported at the annual meeting of the American Academy of Hospice and Palliative Medicine.

For the study, patients with intractable dyspnea received ordinary air or palliative oxygen, which combined air with an increased oxygen concentration of up to 28%. Both treatments were given via nasal cannulae from a blinded concentrator at 2 L per minute for at least 15 hours per day.

Regardless of treatment group, patients with worse breathlessness at baseline were more likely to respond, said Dr. Abernethy, an oncologist and co-chair of the Duke Cancer Care Research Program at Duke University Medical Center in Durham, N.C. After 7 days of treatment, the mean change from baseline in dyspnea symptoms was 1 point for patients with moderate dyspnea (baseline 4-6 points), compared with 2.5 for those with severe dyspnea (baseline 7-10 points).

The findings call into question whether it's necessary to prescribe palliative oxygen in these patients, and suggest that giving air via nasal cannulae is just as good, Dr. Abernethy said. Palliative oxygen is widely used to treat breathlessness, which affects up to 70% of patients with cancer and 90% of those with chronic obstructive pulmonary disease (COPD), and tends to worsen as death nears.

Dr. Abernethy noted that her hospice spends $250,000 per month on oxygen and oxygen concentrators in order to provide palliative oxygen.

"The most important piece in translation is focusing on which patients are likely to get the most benefit," Dr. Abernethy said. "Clearly, it's the patient who is most dyspneic and clearly [the benefits are seen] in the first 24 hours. Whether you should use oxygen or air delivered by nasal cannulae doesn't seem to matter."

The findings will need to be incorporated into the current evidence base and various guidelines, said Dr. Abernethy, noting that recommendations for palliative oxygen vary by guideline group and country. However, the survival benefit of oxygen therapy is well established for severely hypoxic COPD patients (PaO_2 of 55 mm Hg or less).

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Giving air via nasal cannulae may be just as good as palliative oxygen.

A trial is underway to evaluate the use of forced-air fans for treating dyspnea, she said. A review of 47 studies in 2,532 patients with breathlessness and advanced stages of malignant and nonmalignant diseases (mostly COPD) concluded that there was low strength of evidence that acupuncture/acupressure is helpful and not enough data to judge the evidence for fans, music, relaxation, counseling, and psychotherapy (Cochrane Database Syst. Rev. 2008. CD005623 [doi:10.1002/14651858]).

The O_2 Breathe Trial recruited patients with a baseline PaO_2 greater than 55 mm Hg from nine study sites in Australia, the United Kingdom, and the United States. The trial was adequately powered, Dr. Abernethy said, but she noted that it did not have a placebo arm and pulse oximetry was not used. Baseline O_2 saturation was 94%-95%. PaO_2 was measured only at baseline (mean 77 mm Hg).

The patients' mean age was 73 years, 62% were male, 64% had COPD, and 16% had cancer.

In linear regression analyses, patients receiving oxygen therapy were almost twice as likely to have a morning response as were those receiving air (odds ratio 1.86).

The O_2 Breathe Trial was funded by the U.S. National Institute on Aging, Australia's National Health and Medical Research Council, the Doris Duke Charitable Foundation, and the Duke Institute for Care at the End of Life. The authors disclosed no relevant conflicts of interest. ■

A related video is at www.youtube.com/InternalMedicineNews (search for 65658).