PALLIATIVE CARE
CASE OF THE MONTH

Use of Transmucosal Immediate-Release Fentanyl (TIRF) Products

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Volume 12, No. 18 **October 2012**

Case: Ms. P is a 45 y/o woman with metastatic melanoma with a large left groin mass. She has chronic persistent pain in her left leg and groin which has overall been well-controlled with Oxycontin 40 mg q12 with oxycodone 10 – 15 mg every 4 hours as needed. In addition to this chronic pain, she also has an acute breakthrough pain whenever she stands up. This pain is a sharp and severe spasm of her anterior thigh 10/10 in intensity, lasts for 20-30 minutes and is only gradually relieved by applying heat and massaging the thigh. She has tried taking larger doses of oxycodone for this pain but they have not been effective or not taken effect quickly enough. This pain is debilitating and prevents her from being more active as she does not want to get out of bed due to the pain. A trial of transmucosal fentanyl in the form of Actiq 200 uq lozenge was undertaken with good effect. The patient obtained relief within 10-15 minutes and was able to rise from supine with less pain and distress. She continues to use the Actiq lozenge 1-2 times per day for the pain she experiences with rising

Discussion: Fentanyl is a strong mu-opioid receptor agonist. Most physicians are familiar with its use as a transdermal patch for cancer pain and intravenously for procedures and ICU care. However, its low-molecular weight and lipophilic properties also make it suitable for transmucosal administration (unlike other opioids such as morphine, hydromorphone and oxycodone). Transmucosal administration of fentanyl can provide a rapid onset of analgesia which can better match the time course of some breakthrough cancer pain. Time to onset of these products is generally listed as 10 – 15 minutes. TIRF medicines can be particularly helpful for cancer patients who experience pain with dressing changes or draining procedures, and patients who cannot take opioids eternally. Because of their acute onset and potency, transmucosal immediate-release fentanyl (TIRF) medicines are contraindicated in patients who are not already tolerant to opioids. They are only indicated for breakthrough cancer pain in patients already receiving at least the equivalent of 60 mg oral morphine per 24 hours. TIRF medicines should not be used for acute, postoperative pain, or headache pain. Use by patients who are not opioid-tolerant can lead to life-threatening overdose with even a single dose.

Currently, six different transmucosal immediate-release fentanyl (TIRF) products (and their generic equivalents) are available in the US: Abstral sublingual tablet, Actiq oral transmucosal lozenge, Fentora buccal tablet, Lazanda nasal spray, Onsolis buccal soluble film, and Subsys sublingual spray. The licensed TIRF products are generally very expensive (ranging between $17-$120 per dose) and insurance coverage is often limited. Limited comparative data exist to guide clinicians in selecting a specific product. Therefore, selection of a special agent depends on patient characteristics and preferences, cost, and clinician familiarity. The products vary in ease of access from packaging, ease of administration and palatability. Nasal administration may work quicker and be shorter lasting compared with sublingual/buccal routes.

The buccal and sublingual products vary in terms of the amount of medicine that is absorbed directly across the mucosa versus what is swallowed. While about two-thirds of swallowed fentanyl is eliminated by intestinal or hepatic first-pass metabolism, a portion of each dose of buccal or sublingual TIRF medicines represents GI absorption.

Discussion (continued): Absorption from the nasal cavity for the nasally administered products depends on mucosal perfusion which can be effected by the degree of vasoconstriction.

TIRF medicines are not interchangeable with each other, regardless of route of administration. Differences exist in the pharmacokinetics of the various TIRF medicines resulting in clinically important differences in the amount of fentanyl absorbed. Therefore, a 200 uq dose of one product is NOT equivalent to a 200 uq dose of another product. Converting from one TIRF medicine to a different TIRF medicine must not be done on a microgram-per-microgram basis and must be titrated according to the labeled dosing instructions each time a patient begins use of a new TIRF medicine. Generally, the product guidelines suggest waiting 4 hours between each dose and not dosing more than 4 times in 24 hours. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount which can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid-tolerant. All medicines must be kept out of the reach of children and pets. Patients and caregivers must be instructed in their proper use, storage and disposal which vary with the specific product being used. The FDA recently implemented a Risk Evaluation and Mitigation Strategy (REMS) program designed to ensure informed risk-benefit decisions before initiating treatment to ensure appropriate use of TIRF medicines. The purpose of the TIRF REMS Access program is to mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors with the use of TIRF medicines. The program requires all clinicians prescribing TIRF medications must complete a brief on-line education module which is available at www.tirfremsaccess.com.

When prescribing a TIRF medication, the physician must review the safety issues associated with TIRFs and have the patient sign a form documenting that the information was reviewed with them.

Transmucosal immediate-release fentanyl products represent a useful tool in managing certain varieties of cancer breakthrough pain. Their variable pharmacokinetics, high cost and potential risks limit their role to a relatively small subset of cancer patients with specific features of breakthrough pain. These medications are best prescribed by clinicians with expertise in pain management and palliative care.

References:

1) Twycross R, Prommer EE, et al. Fentanyl (transmucosal). J Pain Symptom Manage. 2012 Jul; 44(1):131-49.

2) www.tirfremsaccess.com. Accessed on 11/4/2012.