The Use of Oral Transmucosal Fentanyl Citrate During High-Dose-Rate Gynecologic Brachytherapy

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Gynecologic brachytherapy is a form of cancer treatment in which radioactive sources are placed into the pelvic organs via specialized applicators. Traditional low-dose-rate (LDR) brachytherapy has been performed over several days in a hospital setting. Since the 1990s, high-dose-rate (HDR) brachytherapy has been used increasingly because of its decreased treatment time, outpatient administration, and equal or superior efficacy compared with LDR treatment. However, the management of procedural pain in the radiation oncology setting has not been studied extensively. The purpose of this article is to discuss the use of oral transmucosal fentanyl citrate (OTFC) for the management of pain during gynecologic HDR brachytherapy. OTFC provides noninvasive, rapid analgesia with a low incidence of side effects and may be appropriate for other forms of procedure-related cancer pain.

Since the 1990s, high-dose-rate (HDR) brachytherapy for the treatment of gynecologic malignancies has become increasingly available in the United States. This form of radiation therapy offers distinct radiobiologic, technological, and economic advantages over traditional low-dose-rate (LDR) brachytherapy and usually is performed in outpatient settings (Nag et al., 2000). Gynecologic brachytherapy is initiated by the placement of intracavitary applicators into the uterus and vagina, a process formerly performed under general anesthesia (Gosselin & Waring, 2001; Velji & Fitch, 2001).

In radiation oncology settings, procedural pain is a relatively new phenomenon and has not been well documented or studied. The assessment and treatment of procedure-related cancer pain in outpatient environments pose unique challenges for clinicians. Analgesia is essential to patient comfort and facilitates correct applicator placement, thus improving dose delivery to the target area and decreasing potential toxicity to adjacent critical structures (Thomadsen et al., 1992). The purpose of this article is to discuss the use of HDR tandem and ovoid brachytherapy to treat gynecologic cancers, as well as the administration of oral transmucosal fentanyl citrate (OTFC) to treat pain associated with tandem and ovoid applicator insertion.

Brachytherapy for Gynecologic Malignancies

Radiation therapy is a major treatment modality for most gynecologic cancers. Often given in combination with surgery or chemotherapy, ionizing radiation damages RNA or DNA. Resulting mutations alter cell function or mediate cellular necrosis or apoptosis. Radiation therapy is given in divided doses (fractions) to allow restoration of normal cellular function in surrounding healthy tissues and organs; neoplastic cells have a more limited ability to regenerate following radiation exposure.

In addition to traditional external beam radiation therapy (EBRT), women with gynecologic malignancies often receive brachytherapy to enhance the possibility of cure (Ahmad & Jingran, 2004). Brachytherapy is performed by placing radioactive...
sources within body cavities, tissues, or blood vessels (Gosselin & Waring, 2001). Initially, physicians manually placed radiation sources into patients, exposing themselves to significant doses of radiation. The creation of specialized applicators now allows clinicians to insert radiation sources with greater safety and precision (Nag, 2004). Although brachytherapy delivers high doses of radiation to tumors while sparing surrounding tissues, its broader application has been limited by radiation exposure to staff caring for patients receiving the modality. With traditional LDR brachytherapy, patients were hospitalized in lead-shielded rooms for several days. To limit radiation exposure, family members and medical staff were restricted in the amount of time spent with patients. Therefore, patients experienced pain from applicator devices, as well as social isolation from support people (Fieler, 1997; Velji & Fitch, 2001).

In HDR brachytherapy, a computerized, motor-driven after-loading unit (see Figure 1) feeds radioactive sources by remote control from a lead container, through transfer tubes and into an applicator previously placed in a patient (Gosselin & Waring, 2001). The radiation sources are placed at predetermined anatomical locations, based on computed tomography scans and specialized treatment-planning software. This ensures optimal dose distribution to the tumor site, with a rapidly decreasing amount of radiation to normal surrounding structures (Ahamad & Jhingran, 2004). The benefits of the method include no radiation exposure to hospital staff, markedly decreased treatment time, and decreased risk of applicator movement or displacement. Except for initial treatment, doses can be administered on an outpatient basis within minutes because of the higher activity of the sources (Nag, 2004; Thomadsen et al., 1992).

High-Dose-Rate Brachytherapy Procedure

With HDR tandem and ovoid brachytherapy, a patient is admitted to a hospital for insertion of a cervical sleeve while under general anesthesia. The conical-shaped appliance is inserted into the cervix, is sutured adjacent to the cervical os, and remains in place until all treatments are completed. Next, the HDR applicators are placed; they consist of several components. The tandem is a long, hollow, curved tube that is inserted through the cervical sleeve into the uterus. Correct placement of the tandem allows radiation to be delivered to the uterine fundus, lower uterus, and paracervical tissues. Two ovoids then are inserted individually into the vagina, one in each lateral fornix adjacent to the cervix. An ovoid is a long, hollowed instrument with a cylindrical barrel on one end; the barrel contains tungsten shields, which decrease radiation dosing to the bladder trigone and anterior rectal wall (Fletcher, 1978; Leibel & Phillips, 1998). Finally, a rectal retractor is placed in the vagina posterior to the tandem and ovoids to displace the rectum away from the treatment field.

Correct placement of the HDR applicator (see Figure 2) produces a pear-shaped isodose distribution, which allows the uterus, cervix, and upper vagina to receive high doses of radiation, with effective but decreased amounts to the paracervical and parametrial tissues as well as the regional lymphatics (Fletcher, 1978; Griffiths, Silverstone, Tobias, & Benjamin, 1997). While still under the residual effects of anesthesia, a patient is brought to the radiation oncology department. Treatment planning is performed, the initial dose of radiation delivered, and the tandem and ovoids removed. The patient then is returned to the short-procedure unit for recovery and discharge. Subsequent treatments are delivered on an outpatient basis, and the tandem, ovoids, and rectal retractor are placed immediately prior to HDR treatment.

Studies of Low-Dose-Rate Versus High-Dose-Rate Gynecologic Brachytherapy

Much of the early research comparing LDR and HDR brachytherapy was based on retrospective analyses, single-institution studies, or nonrandomized trials (Arai et al., 1992; Lorvidhaya et al., 2000). The studies were conducted in Asia, where HDR brachytherapy has been practiced for more than 30 years because of the increased incidence of cervical cancer, as well as limited inpatient facilities to perform LDR procedures (Nag et al., 2000).

Patel et al. (1993) conducted a prospective randomized clinical trial comparing LDR to HDR brachytherapy in 482 patients with cervical cancer. The study demonstrated similar outcomes in local control and five-year survival between the treatment modalities, with HDR producing less rectal toxicity than LDR brachytherapy (19.9% versus 6.4%). A more recent prospective
randomized study noted comparable results in local control, relapse-free survival, and three-year survival in 221 patients with cervical cancer treated with HDR or LDR brachytherapy (Lertsan-Puansinchai et al., 2004). A meta-analysis of 21 studies involving more than 9,300 patients receiving HDR or LDR brachytherapy for cervical or endometrial cancer showed that patients with cervical cancer treated with HDR brachytherapy had lower morbidity rates than those receiving LDR treatment. No difference existed in morbidity rates in patients with endometrial cancer treated with HDR versus LDR therapy (Orton, 1993).

Despite the studies showing comparable outcomes between LDR and HDR gynecologic brachytherapy, HDR treatment has only recently gained favor in the United States. Reluctance to adopt this form of treatment may have been related to the paucity of prospective randomized clinical trials (Nag, Orton, Young, & Erickson, 1999). As more radiation oncology departments incorporated HDR brachytherapy into their clinical practices and published their results, variations were noted in implant techniques, dose per fraction, fractionization schedules, and quality assurance. In 2000, the American Brachytherapy Society published clinical practice guidelines for the use of HDR brachytherapy in the treatment of cervical cancer. The guidelines also provided recommendations for pain management during HDR applicator placement but acknowledged that no consensus exists as to which analgesics are most effective (Nag et al., 2000).

**Procedural Cancer Pain**

Although many individuals with cancer are treated effectively for chronic pain, breakthrough pain remains a significant problem. An international survey of pain clinicians indicated that 65% of oncology clients reported breakthrough pain (Caraceni et al., 2004). Untreated breakthrough pain has an adverse impact on psychological and functional status and on quality of life; breakthrough pain also is a predictor of increased resistance to opioid therapy (Mercadante, Maddaloni, Roccella, & Salvaggio, 1992; Portenoy & Hagen, 1990). Portenoy, Payne, and Jacobsen (1999) defined breakthrough pain as an exacerbation of severe pain that is superimposed on chronic yet controlled pain. Although unpredictable, breakthrough cancer pain typically has a sudden onset, reaches maximum intensity in less than five minutes, is described as moderate to severe in intensity, and lasts an average of 30 minutes (Coluzzi et al., 2001).

It can be triggered by voluntary movement (incident pain), an unknown etiology (idiopathic pain), or diagnostic, operative or treatment-related measures (procedural pain). Patients with cancer undergo various painful procedures during the course of diagnosis, treatment, and follow-up care. Unrelieved pain produces multiple signs of physiologic and psychological stress and may increase distress during subsequent procedures (Pasero & McCaffery, 1999).

**Scope of Procedural Pain**

In 1992, the Agency for Health Care Policy and Research (AHCPR) issued guidelines for the management of pain during operative and medical procedures. More recently, the American Pain Society published evidence-based recommendations regarding procedure-related pain in children and adults (Miaskowski et al., 2005). Yet research has suggested that the guidelines are not incorporated fully into clinical practice. A large, prospective, multicenter study of analgesic administration prior to common hospital procedures (e.g., turning, removing drains, tracheal suctioning) revealed that 65% of patients received no pain medications prior to their procedures (Puntillo et al., 2002).

Most studies of procedure-based pain have been conducted in the pediatric population. Children with cancer face multiple painful interventions during diagnosis and treatment. Repeated venipunctures, lumbar punctures, and bone marrow aspirations have demonstrated physical and psychological sequelae in pediatric patients (Kuppenheimer & Brown, 2002). Survivors of childhood leukemia reported that invasive procedures elicited more pain than treatment or than cancer itself (Kazak et al., 1996), and the patients and their parents exhibited symptoms of post-traumatic stress as long as 12 years after completion of therapy (Stuber, Christakis, Houskamp, & Kazak, 1996). In response to such deficiencies, the American Academy of Pediatrics (2002) developed guidelines to provide safe, effective sedation and anxiolysis for painful procedures in children. However, few studies have documented the incidence and prevalence of unrelieved procedure-based cancer pain in adults or measures to prevent it (Miaskowski et al., 2005).

**Procedural Pain in Radiation Oncology**

The treatment of procedural pain in radiation therapy departments poses special challenges for nurses and other clinicians. Few studies have been published about the effects of analgesia during outpatient intracavitary HDR insertion. Smith, Todd, and Symonds (2002) advocated the use of conscious sedation with IV fentanyl and midazolam. The American Brachytherapy Society recommended conscious sedation, paracervical block, or spinal anesthesia but acknowledges that some radiation oncology practices administer no medications (Nag et al., 2000).

When selecting appropriate analgesics to manage procedural pain, healthcare professionals should assess the multidimensional aspects of pain, including the pathophysiologic forces that evoke pain responses. In patients receiving HDR gynecologic brachytherapy, tandem placement in the uterine corpus causes sympathetic stimulation of the hypogastric plexus, leading to cramping visceral pain. The presence of ovoids in the upper vaginal vault elicits parasympathetic stimulation of the

![Figure 2. Tandem and Ovoid Applicator](Image courtesy of Nucletron. Used with permission.)
pelvic splanchnic nerve, with resulting lumbar pain (Loeser, 2001; Smith et al., 2002). Published studies of HDR brachytherapy frequently focus on the technical aspects of treatment but do not disclose pain management methods (Lertsangunsinchan et al., 2004; Patel, Rai, Dip, Mallick, & Sharma, 2005). When considering analgesia for outpatient procedures, the ideal sedative should be noninvasive, be administered easily, provide a rapid onset of action, have a short duration, allow for minimal monitoring by medical staff, and enable prompt patient discharge (Sharar et al., 2002). Oral transmucosal fentanyl citrate (OTFC) has a pharmacologic profile that matches the qualities needed to adequately manage pain in outpatient settings.

Oral Transmucosal Fentanyl Citrate

Fentanyl, in its transmucosal form, is a highly lipophilic, synthetic opioid agonist that binds to mu receptors in the brain and spinal cord, causing analgesia and sedation (Portenoy, Payne, Coluzzi, et al., 1999). Opiate medications simulate the action of endogenous neuromodulators (enkephalins, dynorphins, and endorphins) by binding at opioid receptors to produce pain relief. Opioid agonists are proposed to act on primary afferent fibers in the spinal cord, as well as the periaqueductal gray and rostral ventromedial medulla in the brainstem, to decrease pain perception and autonomic nervous system response to painful stimuli. Opioids provide analgesia with no ceiling effect, but their side effects (including sedation, constipation, and respiratory depression) should be managed preemptively by clinicians (Holden, Jeong, & Forrest, 2005).

OTFC was approved in 1998 for the treatment of breakthrough cancer pain. Marketed under the brand name Actiq® (Cephalon Inc.), OTFC delivers a dose of fentanyl via a sweetened lozenge, which is attached to a plastic applicator unit. The patient applies the OTFC to the buccal mucosa, and approximately 25% of the dose is absorbed rapidly into the bloodstream and quickly becomes systematically bioavailable. The remaining 75% is swallowed and slowly absorbed in the gastrointestinal tract, with approximately one-third of that amount escaping first-pass elimination in the liver. Thus, about 50% of the total OTFC dose is readily bioavailable, with peak plasma concentration in 5–10 minutes (Streisand et al., 1991) and onset of analgesia in an average of 5 minutes, a rate comparable to IV morphine (Lichtor et al., 1999).

Clinical trials of OTFC for the treatment of breakthrough cancer pain generally have revealed a positive efficacy and safety profile (see Table 1). Common side effects attributed to OTFC include sedation (8%–18%), nausea (11%–14%) and dizziness (7%–17%) (Christie et al., 1998; Coluzzi et al., 2001; Farrar, Cleary, Rauck, Busch, & Nordbrock, 1998). The adverse effects often are associated with opioid administration. Although OTFC appears to be an attractive option in pain management in pediatric populations, the incidence of vomiting and pruritis limit its use in children (Klein et al., 2002; Schechter, Weisman, Rosenblum, Bernstein, & Conard, 1995; Streisand et al., 1989). The addition of a 5-HT3 antagonist did not decrease the incidence of postoperative nausea and vomiting in pediatric patients who had received OTFC preoperatively to facilitate anesthesia induction (Binstock et al., 2004). Studies of transmucosal fentanyl use in adults have suggested that no equianalgesic relationship exists between OTFC dosing and medications used for persistent pain (Christie et al.; Payne et al., 2001) or those for breakthrough pain (Farrar et al.; Portenoy, Payne, Coluzzi, et al., 1999). Research has found that optimization of OTFC is best determined by titration alone (Christie et al.; Coluzzi et al.; Portenoy, Payne, Coluzzi, et al.). Practice guidelines for breakthrough pain suggest an OTFC starting dose of 200 mcg in opioid-naïve patients, older adults, patients with a history of pulmonary disease, and those with a history of opioid sensitivity. For opioid-tolerant patients, 400 mcg is an acceptable initial dose. Clinicians are advised to titrate upward until pain is relieved or until unacceptable side effects occur (Aronoff, Brennan, Pritchard, & Ginsberg, 2005).

Analysis of Results

From October 2004–June 2007, 33 patients have used OTFC for HDR tandem and ovoid insertion in the author’s department, a suburban, hospital-based radiation oncology practice that treats approximately 80 patients daily. In addition to the prescribed OTFC dose, women who exhibited marked anxiety when initially instructed about the procedure were asked to administer 1 mg oral lorazepam one hour before reporting to the radiation oncology unit. Lorazepam often is prescribed for medical procedures for its anxiolytic properties, as well as its ability to induce anterograde amnesia (Dunlop, Deen, Lind, Voyle, & Prichard, 1999; Wolanskyj et al., 2000). Of the women who received OTFC, one patient with a concurrent diagnosis of severe postherpetic neuralgia found OTFC to be ineffective in treating procedural pain, perhaps secondary to her long-term use of opioids. Persistent vomiting was noted in another patient with a documented intolerance to opioids; OTFC was discontinued, and the client tolerated the procedure with administration of oral lorazepam and 1% viscous lidocaine applied to the tandem and ovoids prior to insertion. Topical lidocaine has been used previously for bladder mucosal biopsies (Pode, Zylber-Katz, & Shapiro, 1992), as well as mucosal laceration repair in children (Smith et al., 1998). The remaining patients who used OTFC for tandem and ovoid insertion voiced satisfaction with the medication and its novel route of administration. In the author's limited experience, no serious adverse events were noted in opioid-tolerant or opioid-naïve patients. In selecting appropriate initial OTFC doses, evidence-based dosing and assessment guidelines were observed (Aronoff et al., 2005).

Future Research Directions

Radiation oncology is an increasingly technical subspecialty and requires nursing personnel who can complement the complexity of treatment with comprehensive care, education, and counseling of patients and caregivers. Nurses are uniquely qualified to provide information about brachytherapy procedures, anticipated side effects, and self-care activities (Gosselein & Waring, 2001). Teaching should be culturally sensitive, tailored to patients’ education levels, and provided via oral and written instructions (Fieler, 1997; Velji & Fitch, 2001). Pain reassessment during and immediately after each tandem and ovoid insertion is essential to ensure optimal analgesia during subsequent procedures.
### Table 1. Clinical Trials of Oral Transmucosal Fentanyl Citrate

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<th>AUTHOR AND SAMPLE</th>
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<tr>
<td>Christie et al., 1998 (N = 62)</td>
<td>If effective, a single dose of OTFC can be determined by titration; to compare OTFC versus regular rescue medication. Multicenter, randomized, double-blind, dose titration study</td>
<td>Transdermal fentanyl 50–3,000 mcg per hour</td>
<td>Pain intensity was measured before each use of breakthrough medication (usual or OTFC); pain intensity, pain relief, and global satisfaction were measured 15, 30, and 60 minutes after administration of usual medication or OTFC.</td>
<td>Pain intensity was lower and pain relief was higher with OTFC versus regular rescue medication at all intervals (p &lt; 0.0002); global satisfaction scores were higher with OTFC than with usual breakthrough drugs (2.6 versus 2.0, p = 0.0001); 76% of subjects found a safe and effective dose of OTFC; no correlation was found between transdermal fentanyl and OTFC dose.</td>
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<td>Farrar et al., 1998 (N = 89)</td>
<td>To determine whether OTFC is more effective than placebo in treating breakthrough pain. Multicenter, randomized, double-blind, placebo-controlled trial</td>
<td>Oral morphine &gt; 60 mg per day or transdermal fentanyl &gt; 50 mcg per hour; previously titrated to optimal OTFC dose</td>
<td>Sequentially numbered units (seven OTFC and three placebo) were used for each episode of breakthrough pain; usual rescue pain medications were used if relief was inadequate after 30 minutes; pain intensity, pain relief, and use of rescue medications were evaluated 15, 30, 45, and 60 minutes after administration.</td>
<td>Decreased pain intensity and increased pain relief with OTFC versus placebo at all time points (p &lt; 0.0001); subjects were more than twice as likely to use rescue medications when using placebo versus OTFC (34% versus 15%, p &lt; 0.0001); mean global performance evaluation = 1.98 OTFC versus 1.19 placebo (p &lt; 0.0001).</td>
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<tr>
<td>Coluzzi et al., 2001 (N = 134)</td>
<td>To compare OTFC to immediate-release morphine in treating breakthrough pain. Multicenter, randomized, double-blind multiple crossover trial</td>
<td>Equivalent of oral morphine 60–1,000 mg per day or transdermal fentanyl 50–300 mcg per hour; also immediate-release morphine 15–60 mg</td>
<td>Subjects were titrated to effective dose of OTFC, then given 10 prenumbered sets containing one oral and one transmucosal unit. Patients were instructed to use one complete unit for each episode of breakthrough pain and to repeat in one hour if pain recurred or was unrelied. Pain intensity was rated 15 minutes before administration and 15, 30, 45, and 60 minutes after. Pain relief was recorded 15, 30, 45, and 60 minutes after dosing. Global performance was rated 60 minutes after dosing.</td>
<td>Pain intensity was lower with OTFC than MSIR (p &lt; 0.019); pain relief scores were higher with OTFC than with MSIR at each time point (p &lt; 0.011); global medication performance rating was higher with OTFC (2.5 versus 2.1, p &lt; 0.001); 94% of subjects continued OTFC use during an extension of the trial.</td>
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**Note.** Pain intensity was rated from 0 (no pain) to 10 (worst pain imaginable). Pain relief was rated from 0 (none) to 4 (complete). Global satisfaction and performance were rated from 0 (poor) to 4 (excellent). MSIR—morphine sulfate immediate release; OTFC—oral transmucosal fentanyl citrate

The use of nonpharmacologic strategies to reduce procedural pain warrants further investigation. In a phenomenologic study of gynecologic brachytherapy clients, patients noted that their physical distress was not restricted to pain alone, and methods such as massage and position changes were effective in decreasing discomfort and distress. Patients valued nurses who were knowledgeable about the brachytherapy process and possessed the ability to anticipate patient needs and meet those needs in a timely and reassuring manner (Velji & Fitch, 2001). Puntillo (1990) suggested the use of a support person to promote patient comfort. The use of music therapy, guided imagery, and other cognitive strategies also may decrease procedure-related pain.
pain. Such interventions are recommended to enhance but not replace analgesics currently used in pain management (Miaskowski et al., 2005).

In radiation oncology settings, unfamiliarity with procedural pain may hamper efforts to optimally manage that type of pain. A survey of 92 radiation oncologists found that 40% rated pain management in their practice settings as poor to fair, and 72% would initiate a strong opioid only when a patient did not respond to radiotherapy. Physicians may perceive their role as palliating pain by radiotherapeutic measures alone; such self-limitations may prevent comprehensive pain assessment and use of evidence-based guidelines to effectively treat pain (Cleeland, Janjan, Scott, Seiferheld, & Curran, 2000). Procedural pain may be superimposed on other cancer pain syndromes, thus complicating treatment (Portenoy, Payne, & Jacobsen, 1999). Unlike other forms of cancer pain, procedural pain can be anticipated and prevented (Gordon et al., 2005; Punttillo et al., 2002).

OTFC as the primary analgesic during applicator placement is successful for several reasons. OTFC has a pharmacologic profile that correlates with the qualities of procedural pain; its rapid onset and short duration of action allow efficacious, easily administered analgesia (Gordon, 2006). Additionally, the low side-effect profile of OTFC supports research on its use in other procedures commonly performed on patients with cancer, such as central line placement, chest tube insertion, thoracentesis, paracentesis, and bone marrow aspiration and biopsy.

Additional study is necessary to evaluate pain in outpatient cancer settings. Randomized clinical trials to compare the effectiveness of less invasive pain management methods with IV opioids and anesthetics are indicated. A survey of various oncology practices may be valuable to reveal trends in pain management, as well as novel pharmacologic and cognitive strategies to manage procedural pain. Such research has the potential to spur quality improvement and assist nurses and other clinicians in providing effective interventions to treat the complex nature of procedure-based pain in adults with cancer.

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