Current Pain and Headache Reports (2019) 23: 50
https://doi.org/10.1007/s11916-019-0780-2

OTHER PAIN (A KAYE AND N VADIVELU, SECTION EDITORS)

Consensus Perioperative Management Best Practices for Patients on Transdermal Fentanyl Patches Undergoing Surgery

Alan David Kaye[1] · Bethany L. Menard[1] · Ken P. Ehrhardt[1] · Sonja A. Gennuso[2] · Eva C. Okereke[2] · Sridhar R. Tirumala[2] · Charles J. Fox[2] · Elyse M. Cornett[2]

Published online: 21 June 2019

Abstract

Purpose of Review The administration of a transdermal fentanyl patch can be complicated with different pharmacokinetics than other fentanyl preparations.

Recent Findings The medical condition and baseline opioid requirements must all be carefully considered when dosing a fentanyl patch. An advantage of the fentanyl patch is its ability to bypass the gastrointestinal tract and in many patients, provide effective analgesia with minimal side effects. Fentanyl patches must be carefully administered since morbidity and/or mortality can result from the following: Giving higher doses than a patient needs, combining the medication with potent sedatives, or heating a fentanyl patch. The use of a transdermal fentanyl patch for the treatment of acute postoperative pain is not recommended and any patient undergoing a surgical procedure should have the fentanyl patch removed preoperatively.

Summary The current manuscript discusses the history of fentanyl and the fentanyl patch, as well as perioperative considerations, contraindications, current clinical efficacy, and clinical adversities related to the transdermal fentanyl patch. Regarding the heating of a transdermal fentanyl patch, which significantly increases blood levels of fentanyl, it is of the utmost importance that the patch be removed prior to surgery.

Keywords Fentanyl patch · Morphine opioid · Surgery · Transdermal

Introduction

History of Fentanyl

In 1953, Dr. Paul Janssen began his search for a fast-acting potent analgesic. At the time, morphine and meperidine were typically used; however, their actions had a slow onset and narrow therapeutic margins. Furthermore, Dr. Janssen discovered that these compounds did not easily penetrate the central nervous system and concluded that the molecules must be fat or lipid soluble to cross the blood–brain barrier [1]. In developing his novel compound, he initially used the meperidine molecule as a backbone and added a number of different chemical entities to make it more lipid soluble. His first

This article is part of the Topical Collection on *Other Pain*

✉ Elyse M. Cornett
ecorne@lsuhsc.edu

Alan David Kaye
akaye@lsuhsc.edu

Bethany L. Menard
bmenar@lsuhsc.edu

Ken P. Ehrhardt
ehrhardtken@gmail.com

Sonja A. Gennuso
sgennu@lsuhsc.edu

Eva C. Okereke
eokere@lsuhsc.edu

Sridhar R. Tirumala
stirum@lsuhsc.edu

Charles J. Fox
cfox1@lsuhsc.edu

[1] Department of Anesthesiology, LSU Health Sciences Center, Room 656, 1542 Tulane Ave, New Orleans, LA 70112, USA

[2] Department of Anesthesiology, LSU Health Shreveport, 1501 Kings Highway, Shreveport, LA 71103, USA

successful compound was phenoperidine, which was 25 times more potent than morphine; the most potent synthetic opioid of its time. Phenoperidine was introduced in Europe and is still available in some countries today [2].

Dr. Janssen eventually derived fentanyl, which was related to the phenoperidine structure. Fentanyl was 100 times more potent than morphine in animal models and was also 10 times more potent than phenoperidine [1]. At the time, fentanyl was the most lipid-soluble opioid molecule with an octanol/water partition coefficient of 813. Fentanyl had the highest therapeutic window, was the fastest acting, and was also the most potent at the time [2]. Fentanyl is a mu-opioid agonist that binds to receptors in the central nervous system and mimics the effects of endogenous opiates to give its effects of analgesia and euphoria. The fentanyl compound can be visualized in Fig. 1 [3].

Fentanyl was initially used as an intravenous analgesic and is currently used during induction of anesthesia. It is still the most commonly used opioid in anesthesia practices in many countries today [2]. Along with intravenous routes, fentanyl is now available as transmucosal delivery systems, sublingual routes, intranasal formulations, and transdermal applications [2].

Fentanyl Patch

The fentanyl patch was first developed and studied by the pharmaceutical companies Alza and Anestha in the mid-1980s. The fentanyl patch was initially developed with hopes of providing acute pain control in patients after surgery as well as in patients with chronic pain. The transdermal patch was initially studied in acute postoperative pain in opioid-naïve patients; however, side effects included high rates of respiratory depression [4]. The fentanyl patch proved to be much more useful in the treatment of cancer-related pain in patients taking chronic opioids. This use gained its approval by the FDA and regulatory agencies in Europe [5]. The fentanyl patch, also named Duragesic, was most successful due to its ability to maintain a steady-state level of fentanyl concentrations in the blood for 2–3 days with the use of one patch. It showed that the steady state was reached after 14–18 h [4].

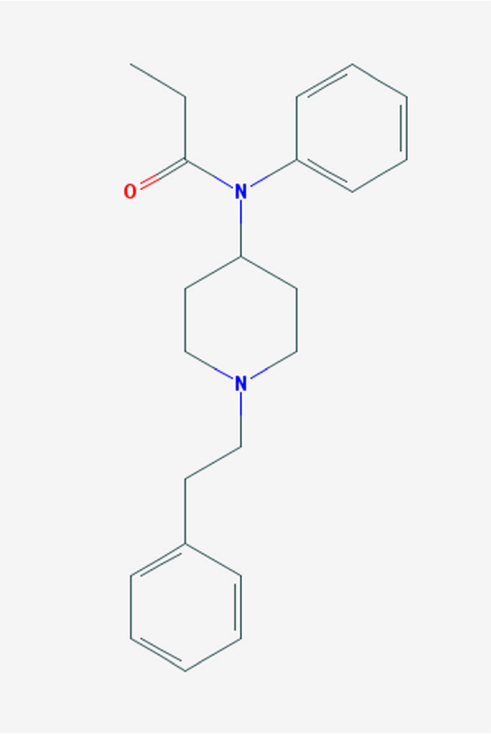

Fig. 1 The fentanyl molecule which is a synthetic, lipophilic phenylpiperdine opioid agonist [3]

Pharmacology

The most common use of fentanyl patches in practice today is in the treatment of chronic pain. Because the fentanyl patch produces a steady state of blood fentanyl concentrations, it is an excellent modality for patients suffering from both cancer and non-cancer chronic pain. The fentanyl patch is roughly equivalent to 75 times the potency of morphine [6]. It is currently available in four different dosages including 25, 50, 75, and 100 μg/h. The hourly rate is the predicted level of fentanyl concentration in the blood at any given time and can be worn for a period of 72 h [7]. After the patch has been applied, fentanyl blood concentration levels increase until they reach a steady state around the 24-h mark. Fentanyl concentrations can remain in this steady state if the fentanyl patch is renewed after 72 h. Changes in blood supply to the area under the fentanyl do not alter concentration levels; however, a sharp increase in body temperature (up to 40 °C) can increase blood levels by as much as 30% [8]. When plasma levels reach as low as 0.2 to 1.2 ng/ml, opioid-naïve patients can experience significant analgesia; however, levels may be much higher in patients using chronic opioids [2]. Levels of fentanyl decline slowly after removal of the fentanyl patch with a half-life of around 17 h [9]. Just as other opioids, the fentanyl patch exerts its effects through mu opioid receptors in the central nervous system. These effects include analgesia, sedation, respiratory depression, and bradycardia, as well as loss of consciousness in higher doses [9]. It also can cause other side effects such as nausea and vomiting and pruritus. Metabolism of fentanyl is through the cytochrome p450 system, specifically CYP 3A4, in the liver. Any other drug that alters the function of CYP3A4 has the potential to alter metabolism of fentanyl and can therefore lead to unexpected blood levels of fentanyl [10].

Fentanyl in Anesthesia

Fentanyl began to be favored over morphine in anesthesiology in the 1980s. Unlike morphine, fentanyl has little, if any,

histamine release and therefore causes no vasodilation and hypotension. Fentanyl also has a faster onset with a shorter duration than morphine [2]. The use of fentanyl also allowed for faster anesthetic inductions and less dramatic blood pressure changes throughout surgery, as well as faster recovery times and time to extubation [5]. With fentanyl's growing population in the anesthesia community, further research began to expand its use. The next recorded use of fentanyl was its addition to spinal and epidural anesthesia once again due to the lipophilic nature of fentanyl [9].

Along with the discovery of the fentanyl patch, fentanyl was also developed as a transmucosal delivery system in the form of lozenges or lollipops as well as the fentanyl patch [2]. Transmucosal delivery systems were used as anesthetic premedication with rapid onset of about 5 to 15 min and a somewhat short duration of action, approximately 1–2 h. By the late 1990s, it also proved useful in the treatment of breakthrough in chronic opioid patients [2]. Other forms of fentanyl transmucosal delivery systems include nasal and sublingual sprays, sublingual tablets, and soluble buccal films and tablets.

Transdermal Drug Delivery

Transdermal drug delivery systems began in the late 1970s with the advent of the scopolamine that was used in the prevention of motion sickness. Nitroglycerin patches gained FDA approval in the 1980s as well as the nicotine patches in the early 1990s [7]. Transdermal fentanyl was approved by the FDA in the early 1990s for the treatment of chronic pain in opioid-tolerant patients [2]. Transdermal drug delivery has many advantages including improved patient compliance. Another particular advantage is that it produces a steady level of blood concentrations and avoids the complications of peaks and troughs of the medication [7].

To understand the pharmacokinetics of the fentanyl patch delivery system, one must first understand the structure of the skin and the layers involved in the absorption and delivery of the medication. The skin is the largest organ of the body and is comprised of multiple layers, with the main layers being the epidermis, the dermis, and the hypodermis. The outer layer, also known as the epidermis, and particularly the stratum corneum, acts as the greatest barrier to drug absorption. Absorption into systemic circulation occurs at the level of the dermis due to the presence of large capillary beds in this layer [11].

Transdermal drugs must pass through multiple areas, which have both lipophilic and hydrophilic components. Because fentanyl is both lipid and water soluble along with a low molecular weight, it is an ideal drug for transdermal administration [7]. As the drug travels through the different layers of the skin, the drug concentration gradient begins to develop and drugs move down that gradient where it is absorbed into capillaries in the dermis and gets into systemic circulation [7]. The movement of the drug down the gradient is responsible for the time until effective drug levels. A drug reservoir can also form in the stratum corneum and can affect the rate of drug decline after a patch has been removed [7].

Currently, there are two types of transdermal fentanyl delivery systems. The first type was the Duragesic reservoir patch. Reservoir-type patches have a rate-controlling membrane that separates the drug reservoir from the skin. The other type of patch more commonly used today is the DTrans, which is a matrix-type patch. The matrix design has the drug imbedded into the adhesive of the patch and allows for constant delivery of the drug. Drug dosage is dependent on the amount of drugs contained in the matrix as well as the surface area to which it is applied [7]. Due to the unique pharmacokinetics of the transdermal delivery system, particular care should be taken with patients who have severe side effects or patients that may require dose adjustments.

Surgical Management of Transdermal Fentanyl Patch

Preoperative

To date, there are no practice management standards or guidelines from the American Society of Anesthesiologists for the perioperative management of transdermal fentanyl patches. However, current studies are evaluating the use of transdermal fentanyl along with regional anesthesia for intraoperative and postsurgical analgesia in adult patients.

Intraoperative

Various studies have previously examined the possibility of the use of a transdermal fentanyl patch as a viable alternative to intravenous fentanyl for surgical pain. Single nucleotide polymorphisms are responsible for interindividual variability of both intravenous and transdermal fentanyl pharmacokinetics. Following intravenous administration in surgical patients, there is a high extravascular volume of distribution. Following the application of a transdermal fentanyl patch, the average bioavailability of fentanyl is estimated at 92% [12]. One study involving women undergoing gynecological exploratory laparotomy consisted of two fentanyl patches (40 and 60 cm^2) that were applied 2 h prior to incision. Three to six hours following patch application, therapeutic fentanyl concentration satisfactory for pain control was achieved [13]. The conclusions of other studies demonstrate efficacy of a transdermal fentanyl patch 2–3 h prior to surgery [14–16].

Although these pain scores are satisfactory, there have been case reports of excessive opioid administration following the use of transdermal fentanyl patch and patient-heating devices during surgery [17•]. As the skin temperature increases, there

is a gradual increase of cutaneous blood flow [18]; and a body temperature increase to 40 °C may increase the absorption rate by one-third with studies demonstrating significant increases in serum fentanyl levels [12, 19••]. In a study by Moore et al., an external heating blanket applied during the first 10 h of treatment increased serum fentanyl levels by 120–184%, while levels increased minimally at 26–36 h of treatment demonstrating the greatest increase in the first 10 h of patch placement. Therefore, it is critical that even though efficacy has been demonstrated, policies should be considered to remove any transdermal fentanyl patches preoperatively as a best practice standard, and outside the operating room, direct exposure to saunas, heat lamps, hot tubs, and electric blankets should always be avoided [20••].

Postoperative

Overall, when applied 2–3 h prior to surgical incision, the transdermal fentanyl patch provides equivalent analgesic efficacy to that of morphine for adult patients who underwent major abdominal, thoracic, or orthopedic surgery [15, 16, 21]. Studies which concluded that the transdermal fentanyl patch did not provide adequate analgesia did not allow adequate application time for an effective serum level of fentanyl to be achieved [22, 23•]. The patch should not be used to treat acute postoperative pain.

Dosing Considerations

General Warnings

At present, there are no clear dosing recommendations for patients undergoing surgery at this time, and because of potential complications with heating blankets intraoperatively, strong consideration should be given to establish policies requiring removal prior to any surgical procedure.

Analgesia Studies One of the studies with satisfactory analgesia included 3 groups of patients: a placebo group, a group that received a 2.5-mg fentanyl patch, and a group that received a 5-mg fentanyl patch [15]. Adequate pain control was noted in both groups of patients that received application of the 2.5-mg patch and the 5-mg patch. The cancer-related chronic pain literature recommends that initial dosage should not exceed 25 μg/h in opioid-naïve patients and in the elderly or severely debilitated patients taking less than 135 mg/day oral morphine or its equivalent [12]. They further recommend that the transdermal fentanyl patch be applied to an intact, hair-free zone of the skin. If a patient is currently on morphine, use the manufacturer's recommended conversion ratio to personalize transdermal fentanyl patch dosing.

Contraindications

The transdermal fentanyl patch is contraindicated in pediatric patients less than 12 years old and all patients who weigh less than 110 lbs. (50 kg). Transdermal fentanyl patches are currently contraindicated in patients with acute postoperative pain; however, with proper application 2–3 h before surgery, it has been shown to provide adequate pain relief.

As compared to intravenous fentanyl and other narcotics, there seems to be a decreased incidence of nausea, vomiting, constipation, and hypoventilation. Additional adverse effects include edema, erythema, papules, and itching at the skin site [12].

There are also precautions for patients with severe COPD, or any significant lung disease. Chronic obstructive pulmonary disease patients, cor pulmonale patients, or patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression are at risk of respiratory depression. Respiratory depression is more common especially when initiating therapy with a fentanyl patch in these high-risk patients. These high-risk patients tend to have a depressed respiratory drive to the point that apnea can occur. Elderly, cachectic, or debilitated patients have a tendency toward altered metabolism of the fentanyl patch due to their poor body fat stores, muscle wasting, or altered clearance [24]. Cachectic patients, according to a few reports, may not have any improvement in pain with increase of dosage strength of the fentanyl patch. If a cachectic patient has not responded to the dose increase of the fentanyl patch, the last effective dose of the fentanyl patch should be used, then an alternative rescue opioid or an alternative opioid therapy may be considered.

Anesthetic Management

The anesthetic management of patients on the transdermal fentanyl patch can be challenging. The transdermal fentanyl patch has pharmacokinetic variability between patients as described above. Even for the same patient (and as mentioned above), an elevated body temperature can increase the fentanyl absorption by about one-third [25, 26]. Therefore, a patient that has heated blankets or a forced air warmer on for surgery would have increased absorption of the transdermal fentanyl patch, which could present with apnea and delayed emergence, and numerous patients have died as a result. Also, the use of the fentanyl patch with any drug that inhibits the cytochrome P450 system can increase fentanyl plasma concentrations and lead to respiratory distress, prolonged awakening, and patient overdose. Even certain drugs that are given in the perioperative period, such as ciprofloxacin, could prolong the transdermal fentanyl patch making these complications more likely. Given all these potential complications and interactions which can occur under anesthesia in the

perioperative period, this group believes strongly that a fentanyl patch should be discontinued on the day of surgery and alternative modes of opioid analgesia employed.

Titrating

When deciding whether to titrate or to increase the dose of transdermal fentanyl, the timing of its medication release and serum concentrations must be considered. According to the prescribing information for the fentanyl patch, the initial dose may be increased after 3 days depending on a daily dose of additional opioids needed for analgesia [24]. For some cases, it can take up to 6 days for this drug to reach its steady state. Therefore, it is recommended that the patch be worn through two patch applications before the dose is adjusted up. Even after transdermal fentanyl patch removal, it takes some time for the serum concentration of fentanyl to fall. This becomes important to remember especially when trying to transition to another opioid as the addition of another opioid too early could result in fatal opioid overdose. It is recommended that, after removal of the fentanyl patch, one should wait a time period of 24 h or longer before initiating full replacement doses of another opioid [27]. It has been shown that the absorption of transdermal fentanyl is 47% complete at 24 h, 88% complete at 48 h, and 94% complete at 72 h [28, 29]. Therefore, it is recommended that the amount of rescue medication used on days 2 and 3 of patch application should determine whether the dose of the fentanyl patch should be titrated up. If the patient requires greater than three doses of rescue medication in a 24-h period, then the dose of the patch on the next application should be increased [27].

Demonstrated Clinical Efficacy of the Fentanyl Patch

Knee Surgery

The efficacy of transdermal fentanyl patches has been studied in many different types of procedures with varying results. These patches have been studied to assist with analgesia in painful surgeries, such as total knee arthroplasties. Pain control is important in total knee arthroplasty surgeries because it decreases patients' time in the hospital, helps promote early ambulation, and decreases side effects such as deep vein thrombosis and infection [14]. In a 2014 study by Sathitkarnmanee et al., transdermal fentanyl was studied in total knee arthroplasties to decrease the amount of morphine given after the operation [14]. Transdermal fentanyl has a peak effect of 15 h so fentanyl patches consisting of 50 mcg/h were applied 10–12 h prior to surgery in this study. Pain scores and morphine consumption were studied 48 h after the surgery. The study found that transdermal fentanyl decreased both pain scores and opioid consumption at 24 h and 48 h after total knee arthroplasty with a p value of less than 0.001 [14]. Study limitations include a small sample size, which made the study unable to determine the risk of respiratory depression. A different 2015 study by Matsumoto et al. studied the difference of postoperative pain control and ambulation between groups of patients receiving transdermal fentanyl compared to non-steroidal anti-inflammatories (NSAIDs) after total knee arthroplasty [30•]. This study concluded that muscle strength was significantly greater on postoperative day 7 and day 14 in the patients who received transdermal fentanyl compared to NSAIDs [30•].

Forefoot Surgery

Fentanyl patches have been studied in other surgeries with painful postoperative courses such as forefoot surgeries. Hallux valgus, hallux rigidus, or any forefoot surgery can cause severe pain in patients for up to 3 days. In a 2014 study, Merivirta et al. studied the use of transdermal fentanyl patches on postoperative pain scores and opioid consumption after forefoot surgery [23•]. In this study, 60 patients were divided randomly and given either fentanyl patches of 12 mcg/h or a placebo patch for postoperative pain management. Every 6 h, pain scores of patients were documented as well as consumption of rescue opioids. Oxycodone was the medication of choice given to patients as needed for pain. A multimodal regimen of acetaminophen and ibuprofen was given to both groups of patients in the study. The amount of this rescue oxycodone was calculated as the primary measure to determine the efficacy of transdermal fentanyl patches versus placebo [23•]. The study concluded that a transdermal fentanyl patch of 12 mcg/h did not significantly decrease the total rescue dose of oxycodone or the pain scores of patients after forefoot surgery when given with multimodal analgesia [23•].

Head and Neck Cancer

Accounting for 5% of malignant cancer in human beings, head and neck cancer causes severe pain in the majority of patient populations and is often inadequately treated [31•]. These cancers do not only cause pain but can also lead to dysphagia, dysarthria, and weight loss. Because patients with these cancers often cannot tolerate oral medications, transdermal fentanyl patches are a resourceful mechanism of pain management for these patients by bypassing the gastrointestinal system. Fentanyl patches control pain without the need to swallow or to establish intravenous access for medication consumption [31•]. Head and neck cancer patients often suffer a decreased quality of life due to inability to speak, swallow food, drink liquids, and adequately control their pain.

Transdermal fentanyl patches give these patients a method to treat pain and aid in increasing their quality of life as they endure the rigors of chemotherapy, radiation, and surgeries [31•].

Ophthalmic Surgery

Transdermal fentanyl patches have also displayed a role in relieving pain after ophthalmic surgeries. In a 2014 study by Lee et al., fentanyl patches were studied for their efficacy in postoperative pain management after photorefractive keratectomy [32]. During this retrospective study including 199 female patients, half of the patients received tramadol (37.5 mg) combined with acetaminophen (325 mg) twice daily while the other half of the patients received a transdermal fentanyl patch of 12 mcg/h immediately after the procedure [32]. Postoperative pain was rated by patients using the visual analog scale for 3 days after the surgeries. This study depicted a statistically significant reduction in pain score in the patient population treated with the transdermal fentanyl patch compared to the group of patients treated with an oral combination of tramadol and acetaminophen [32]. Although the transdermal fentanyl group did experience more adverse effects, most of the side effects were nausea, and the fentanyl patch group did not experience any serious or terminal adverse events [32]. The effectiveness of this study showed that transdermal fentanyl could be an effective option for pain control for other eye procedures due to its constant distribution of transdermal medication.

Major Abdominal Surgery

Transdermal fentanyl patches can also treat pain after major abdominal surgeries. In a 2015 study by Arshad et al., transdermal fentanyl patches were compared to transdermal buprenorphine in treating postoperative pain after major abdominal surgeries under general anesthesia [33]. A total of 60 patients were monitored for 3 days after surgery. Half of these patients received transdermal fentanyl patches at 25 mcg/h and the other half used buprenorphine at 10 mcg/h for pain control [33]. Pain scores using the visual analog scale were monitored on the first, second, and third day after the procedure. The study found statistically significant decreased pain scores in the group of patients using the transdermal fentanyl patches compared to the patient using the transdermal buprenorphine patches [33]. The main side effects seen in both groups at similar rates were nausea and vomiting, but no serious adverse side effects were noted. Although buprenorphine is a cheaper medication, and it could be argued as more cost conscious, transdermal fentanyl patches proved to be a better agent for analgesia in this study [33].

Oral Surgery

The use of transdermal fentanyl patches prior to oral surgery for removal of impacted third molars have been trialed in Eastern Europe since removal of impacted molars has been associated with severe postoperative pain. Patients receiving the transdermal fentanyl patches have had a reduced postoperative pain score versus those receiving the placebo. It was noted that postoperative pain had been reduced up to 24 h after the surgery was performed in the patients receiving the patch compared to the placebo [34].

Shoulder Surgery

Previous randomized controlled trials have compared patients receiving fentanyl patches to patients receiving a bupivacaine infusion for postoperative pain management for shoulder arthroscopy. The results of the study showed a reduced need for breakthrough analgesia with the fentanyl patch group compared to those who received a continuous infusion of bupivacaine. Consequently, this has shown that transdermal fentanyl administration proves to be a safe, effective form of postoperative analgesia in patients with minimal side effects [35].

Transdermal Fentanyl Patches as an Adjuvant to Paravertebral Block for Analgesia for Breast Cancer Surgery

A double-blind randomized study compared two groups of patients: group 1—administered a 25 μg/h fentanyl patch administered 3 h prior to surgery, with a paravertebral block comprising of 20 ml of 0.25% bupivacaine administered between T1–6 levels, prior to the induction of general anesthesia for breast cancer surgery—versus group 2—a sole paravertebral block administered prior to induction for postoperative pain [36]. The fentanyl patch group had reduced time to first postoperative opiate use for up to 24 h as well as significantly less total postoperative opiate use in this group. Additionally, there has been a reduction in postoperative adverse side effects with the combination of transdermal fentanyl patches and paravertebral blocks, in particular, nausea and vomiting as well as decreased hypertensive response secondary to pain. Furthermore, patients have reported decreased postoperative pain scores up to 48 h after surgery in patients with the fentanyl patches compared to those without the patch [36].

Demonstrated Clinical Morbidity and Mortality Related to the Fentanyl Patch

Patient Death Related to Transdermal Fentanyl Patch

There is an increased risk of respiratory depression when concomitant medications are administered with the fentanyl patch. Medications that have a similar mechanism of action such as other opioids as well as other medications that affect the metabolism of opioids, need to be reviewed prior to application of fentanyl patches. One report discussed a patient who should have had an application of a 50 μg/h patch for postoperative pain control, but was mistakenly administered a 75 μg/h fentanyl patch [37]. The patient also was administered medications which inhibited the CYP3A4 system, which is responsible for the metabolism of opiates. The patient was also receiving patient-controlled analgesia (PCA) with opiates and as a result had been given a very high dose of opiates, leading to respiratory depression, followed by cardiovascular arrest and death. Consequently, the clinician must be cognizant of the dose of the medication to be administered as well as review all medications prior to administration of the fentanyl patch that can affect the metabolism of the opiate to be administered in order to prevent adverse effects and complications from patch administration and protect the safety of the patient.

As stated above, fentanyl patches should not be prescribed for acute pain and should be used with extreme caution in opioid-naïve patients. A 47-year-old opioid-naïve man died 1 day post-discharge after using a prescribed fentanyl patch for postoperative pain following spinal surgery [38]. And, as mentioned earlier, heat can also cause rapid absorption of fentanyl. An opioid-naïve 77-year-old woman was found deceased with multiple fentanyl patches on her skin and a heating pad over one of the patches [39]. Furthermore, a 37-year-old man was found deceased by his girlfriend 1 day after applying a 0.75-mg fentanyl patch that was prescribed to him for back pain that was not relieved by his acetaminophen–hydrocodone prescription [40].

Child Death Related to Fentanyl Patch

There is also the potential for the fentanyl patch to mistakenly cause death in unintended persons [41]. This is important for health care providers to consider when prescribing the fentanyl patch, as the ease and convenience of a patch for drug delivery is what can cause these unfortunate outcomes. The potential for a child to have unintended access to the patch should be a factor in determining whether the fentanyl patch is the right choice for a patient.

For example, in 2013, a 15-month old boy died when he accidentally orally ingested a fentanyl patch that was prescribed to his mother to treat her multiple sclerosis symptoms. The mother and the boy were napping together and it is unknown how the patch was orally ingested by the boy. [41]. A 2-year-old boy died after ingesting a fentanyl patch that was attached to his toy truck. He was playing with the truck at his grandmother's long-term care facility, which is how the patch got stuck to his toy truck [42]. A 1-year old girl was found deceased 2 h after she was put to bed and it was determined that she accidentally swallowed a fentanyl patch that she had found on the floor. [43]. There are also reports of teens abusing the patches by chewing them, which causes large amounts of fentanyl to be rapidly released by disrupting the integrity of the patch matrix [44]. In all of these cases, oral ingestion was the cause of death as fentanyl is more rapidly absorbed through buccal mucosa as compared to transdermal absorption (a 30-fold increase).

Children have also overdosed from skin contact with fentanyl patches. A 4-year-old boy died after placing a discarded fentanyl patch on his skin (he thought it was a bandaid) [45]. Another unfortunate incident occurred when a mother placed a patch on her 6-year-old child who complained of neck pain after a car accident. The child was found deceased the next morning [46].

Magnetic Resonance Imaging

There are some manufacturers who have developed their fentanyl patches with the addition of aluminum or other metals in the non-adhesive backing of the patch. These metals can become heated by the magnet in the magnetic resonance imaging (MRI) machine and can cause skin burns in these patients with a transdermal fentanyl patch in place. It has been noted that the increased risk of burns occurs in inpatient versus outpatient MRI. Therefore, it is recommended that the patch be removed prior to performing the MRI in order to prevent the incidence of burns and reapplication of the patch after the MRI has been performed [47].

Suicide

One unique case report discussed suicide by fentanyl patches. A 42-year-old woman, suffering from cardiac arrest with 11 100 μg/h patches on her chest, was found at home with a suicide note. She was pronounced dead at the hospital [48]. This case report was written to bring awareness to the high rates of suicide among chronic pain patients. Medical professionals should be cognizant of high-risk patients who are also prescribed fentanyl patches.

Summary

Opioids are a mainstay of acute pain management during surgical interventions. Traditionally, intravenous fentanyl is one of the commonly used medications intraoperatively to treat

acute surgically induced pain. However, as medicine evolves and pharmacological advances progress, there are currently a variety of formulations of fentanyl available that show promise as an alternative to intravenous administration. Fentanyl has low molecular weight, and high lipid solubility and potency. In fact, its potency is up to 100 times the potency of morphine. This profile made fentanyl a great candidate for the development of a transcutaneous delivery modality. Transdermal fentanyl patches are known to deliver fentanyl at a constant rate of 25 μg/h, 50 μg/h, 75 μg/h, and 100 μg/h and are replaced every 72 h [12]. It is most extensively studied and used in the adult chronic cancer-related pain patients.

Based on the potential to heat a transdermal fentanyl patch intraoperatively, it is extremely important to appreciate the high risk of continuing the patch during surgery. The authors of this manuscript strongly recommend removing the transdermal fentanyl patch prior to surgery and to employ other opioid agents intraoperatively as needed. Postoperatively, fentanyl transdermal patches are not indicated for acute pain; and therefore, alternative analgesics should be utilized with consideration as to the duration of a previous patch, its extended duration of action, and the potential for additive and/or synergistic effects with additional medications. Caution should also be used when prescribing fentanyl patches to individuals with children.

Compliance with Ethical Standards

Conflict of Interest Bethany L. Menard, Ken P. Ehrhardt, Sonja A. Gennuso, Eva C. Okereke, Sridhar R. Tirumala, Charles J. Fox, and Elyse M. Cornett declare no conflict of interest. Dr. Kaye is on the Speakers Bureau for Depomed, Inc., and Merck.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Stanley TH, Egan TD, Van Aken H, Jannssen J. Entrepeneur extraordinaire, innovative scientist, and significant contributor to anesthesiology. Anesth Analg 20018. 2008;106:451–62.
2. Stanley TH. The fentanyl story. J Pain Elsevier Ltd; 2014;15:1215–1226.
3. Imagefly @ Pubchem.Ncbi.Nlm.Nih.Gov.
4. Duthie DJ, Rowbotham DJ, Wyld R, Henderson PDNW. Plasma fentanyl concentrations during transdermal delivery of fentanyl to surgical patients. Br J Anaesth. 1988;60:614–8.
5. Stanley TH. The history of opioid use in anesthetic delivery. In: Eger EII, Saidman LJWR, editors. Wondrous story anesth: Springer International Publishing; 2014.
6. Foley P, Henderson A, Bissonette E, Wimer Gina FS. Evaluation of fentanyl transdermal patches in rabbits: blood concentrations and physiologic response. Comp Med. 2001;51:239–44.
7. Margetts L, Sawyer R. Transdermal drug delivery: principles and opioid therapy. Contin Educ Anaesthesia, Crit Care Pain. Â© The Board of Management and Trustees of the British Journal of Anaesthesia [2007]. All rights reserved. For permissions, please email: journals.permissions@oxfordjournals.org; 2007;7:171–176.
8. Muijsers RBR W, AJ. Transdermal fentanyl. An updated review of its pharmacological properties and therapeutic efficacy in chronic cancer pain control. Drugs2. 2001;61:2289–2307.
9. Bailey PLST. Intravenous opoiod anesthetics. In: Miller R, editor. Mill Anesth. 4th ed. Philadelphia: Churchill Livingston; 1994.
10. Ellenhorn J. Ellenhorn's medical toxicoloy. 2nd ed. Baltimore: Williams & Wilkins; 1997.
11. Wickett RR, Visscher MO. Structure and function of the epidermal barrier. Am J Infect Control. 2006;34:98–110.
12. Muijsers RBR, Wagstaff AJ. Transdermal fentanyl. Drugs. Springer International Publishing; 2001;61:2289–2307.
13. American Society of Anesthesiologists R, Kreitzer JM, Reinhart D, Sebel PS, Bowie J, Freedman G, et al. Anesthesiology. Anesthesiol. J. Am. Soc. Anesthesiol. [American Society of Anesthesiologists, etc.]; 1995.
14. Sathitkarnmanee T, Tribuddharat S, Noiphitak K, Theerapongpakdee S, Pongjanyakul S, Huntula Y, et al. Transdermal fentanyl patch for postoperative analgesia in total knee arthroplasty: a randomized double-blind controlled trial. J Pain Res Dove Press; 2014 cited 2018 Oct 1];7:449–454. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25120375
15. Indian Society for Study of Pain. Indian Journal of Pain. Medknow Publications and Media Pvt Ltd;
16. Niyogi S, Bhunia P, Nayak J, Santra S, Acharjee A, Chakraborty I. Efficacy of transdermal buprenorphine patch on post-operative pain relief after elective spinal instrumentation surgery. Indian J Anaesth Wolters Kluwer – Medknow Publications; 2017;61:923–929.l
17.• Frölich M, Giannotti A, Modell JH. Opioid overdose in a patient using a fentanyl patch during treatment with a warming blanket. Anesth Analg. 2001;93:647–8. **This is an important manuscript that discusses fentanyl patch overdose with the use of a warming blanket. This is important an important concept for all health care providers.**
18. Song CW, Choi IB, Nah BS, Sahu SK, Osborn JL. Microvasculature and perfusion in normal tissues and tumors. Springer, Berlin, Heidelberg; 1995. p. 139–156.
19.•• Hao J, Ghosh P, Li SK, Newman B, Kasting GB, Raney SG. Heat effects on drug delivery across human skin. Expert Opin Drug Deliv [Internet]. 2016 [cited 2018 Oct 3];13:755–68. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26808472
20.•• Moore KT, Sathyan G, Richarz U, Natarajan J, Vandenbossche J. Randomized 5-treatment crossover study to assess the effects of external heat on serum fentanyl concentrations during treatment with transdermal fentanyl systems. J Clin Pharmacol [Internet]. 2012 [cited 2018 Oct 3];52:1174–85. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21878578. **This is a clinical trial to confirm the effects of heat on the delivery of fentantl via transdermal patch.**
21. Scott LJ. Fentanyl iontophoretic transdermal system: a review in acute postoperative pain. Clin Drug Investig Springer International Publishing; 2016;36:321–330.
22. Sevarino FB, Naulty JS, Sinatra R, Chin ML, Paige D, Conry K, et al. Transdermal fentanyl for postoperative pain management in

patients recovering from abdominal gynecologic surgery. Anesthesiology. 1992;77:463–6.

23.• Merivirta R, Alanen J, Haapoja E, Kuusniemi K, Pitkanen M, Kovisto M. Postoperative pain management with transdermal fentanyl after forefoot surgery: a randomized, placebo-controlled study. J Pain Res [Internet]. 2015 [cited 2018 Oct 1];8:39. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25653553. **This is another important research study that confirms the effects of heat on transdermal fentanyl delivery.**

24. DURAGESIC Full US prescribing information. Acessed 9/17/2018.

25. Carter KA. Heat-associated increase in transdermal fentanyl absorption. Am J Health Syst Pharm. 2003;60:191–2.

26. Muijsers RB, Wagstaff AJ. Transdermal fentanyl: an updated review of its pharmacological properties and therapeutic efficacy in chronic cancer pain control. Drugs. 2001;61:2289–307.

27. McPherson MLM, American Society of Health-System Pharmacists. Demystifying opioid conversion calculations : a guide for effective dosing.

28. Portenoy RK, Southam MA, Gupta SK, Lapin J, Layman M, Inturrisi CE, et al. Anesthesiology. Anesthesiol J Am Soc Anesthesiol [American Society of Anesthesiologists, etc; 1993;78:36–43.

29. Marquardt KA, Tharratt RS, Musallam NA. Fentanyl remaining in a transdermal system following three days of continuous use. Ann Pharmacother. 1995;29:969–71.

30.• Matsumoto S, Matsumoto K, Iida H. Transdermal fentanyl patch improves post-operative pain relief and promotes early functional recovery in patients undergoing primary total knee arthroplasty: a prospective, randomised, controlled trial. Arch Orthop Trauma Surg. 2015 [cited 2018 Oct 1];135:1291–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26112273, 1297. **This manuscript is an important discussion on the positive effects of transdermal fentanyl patches.**

31.• Giusti R, Bossi P, Mazzotta M, Filetti M, Iacono D, Marchetti P. The use of fentanyl in pain management in head and neck cancer patients: a narrative review. Br J Pain. 2018 [cited 2018 Oct 1];12:155–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30057760. **This is a recent review on the effects of the transdermal fentanyl patch on head and neck cancer.**

32. Lee YW, Kim YJ, Kim JM, Bae JH, Choi CY. Efficacy and safety of transdermal fentanyl in the control of postoperative pain after photorefractive keratectomy. J Ocul Pharmacol Ther. 2014 [cited 2018 Oct 1];30:783–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25029377

33. Arshad Z, Prakash R, Gautam S, Kumar S. Comparison between transdermal buprenorphine and transdermal fentanyl for postoperative pain relief after major abdominal surgeries. J Clin DIAGNOSTIC Res. 2015 [cited 2018 Oct 1];9:UC01–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26816973

34. Todorovic V-S, Vasovic M, Andric M, Todorovic L, Kokovic V. Efficacy of fentanyl transdermal patch in pain control after lower third molar surgery: a preliminary study. Med Oral Patol Oral Cir Bucal. Medicina Oral S.L; 2016 [cited 2018 Oct 1];21:e621–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27475691

35. Merivirta R, Äärimaa V, Aantaa R, Koivisto M, Leino K, Liukas A, et al. Postoperative fentanyl patch versus subacromial bupivacaine infusion in arthroscopic shoulder surgery. Arthrosc J Arthrosc Relat Surg. 2013 [cited 2018 Oct 1];29:1129–34. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23809446

36. Bakeer A, Abdallah N. Transdermal fentanyl as an adjuvant to paravertebral block for pain control after breast cancer surgery: a randomized, double-blind controlled trial. Saudi J Anaesth. 2017 [cited 2018 Oct 1];11:384. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29033716

37. Rebecca Summey-Lowman, MBA, RD, LD, CPHRM C, David T. Stewart Jr MD. Hospital employees implicated in fentanyl death | MagMutual. MagMutual. [cited 2018 Oct 1]. Available from: https://www.magmutual.com/learning/claimslesson/hospital-employees-implicated-patient's-death-fentanyl-toxicity

38. Neary B. Relatives of Montana man sue hospital over opiate patch death [Internet]. Insur. J. 2013 [cited 2018 Oct 2]. Available from: https://www.insurancejournal.com/news/west/2013/07/29/299860.htm

39. ISMP medication safety alert. New fentanyl warnings: more needed to protect patients. ISMP. 2005 [cited 2018 Oct 2]. Available from: https://www.medscape.com/viewarticle/510963

40. The Journal of Family Practice. 2 analgesic calamities death by fentanyl patch. 2011. Available from: https://www.mdedge.com/sites/default/files/Document/September-2017/6012JFP_Verdicts.pdf.

41. Institute for Safe Medication Practices (ISMP). Fentanyl patch fatalities linked to "bystander apathy": we all have a role in prevention! | Institute For Safe Medication Practices. 2013 [cited 2018 Oct 2]. Available from: https://www.ismp.org/resources/fentanyl-patch-fatalities-linked-bystander-apathy-we-all-have-role-prevention.

42. National Alert Network (NAN). Proper disposal of fentanyl patches is critical to prevent accidental exposure. 2012. Available from: www.ismp.org/docs/Fentanyl-.

43. Teske J, Weller J-P, Larsch K, Tröger HD, Karst M. Fatal outcome in a child after ingestion of a transdermal fentanyl patch. Int J Legal Med. 2007 [cited 2018 Oct 2];121:147–151. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17115172

44. Faust AC, Terpolilli R, Hughes DW. Management of an oral ingestion of transdermal fentanyl patches: a case report and literature review. Case Rep Med. 2011 [cited 2018 Oct 2];2011:1–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21629807

45. Consumer Med Safety. A top 10 list: protecting young children from medicine mishaps - Consumer Med Safety. 2012 [cited 2018 Oct 2]. Available from: http://www.consumermedsafety.org/medication-safety-articles/item/602-a-top—10-list-protecting-young-children-from-medicine-mishaps.

46. The New York Times. Foster mother's pain patch is believed responsible in 6-year-old girl's death - The New York Times. 2008 [cited 2018 Oct 2]. Available from: https://www.nytimes.com/2008/05/20/nyregion/20patch.html.

47. Kuehn BM. FDA warning: remove drug patches before MRI to prevent burns to skin. JAMA. 2009 [cited 2018 Oct 1];301:1328. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19336702

48. LoVecchio MPH F DO, Ramos L. Case report suicide by Duragesic transdermal fentanyl patch toxicity. Am J Emerg Med. 2011 [cited 2018 Oct 2];29:131.e1–131.e2. Available from: www.elsevier.com/locate/ajem