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Transdermal Fentanyl: Pharmacology and Toxicology- A review

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Abstract

This review article provides evaluate the underlying pharmacology, safety, and misuse/abuse of transdermal fentanyl, one of the cornerstone pharmacotherapies for patients with chronic pain. Fentanyl is a high-potency opioid that has many uses in the treatment of both acute and chronic pain. Intentional or unintentional misuse, as well as abuse, may lead to significant clinical consequences, including death. It also potential pitfalls associated with transdermal fentanyl, although these have not been completely effective in preventing life-threatening adverse events and fatalities related to its inappropriate use. Clinically consequential adverse effects may occur unexpectedly with normal use of transdermal fentanyl, or if misused or abused. Misuse and therapeutic error may be largely preventable through better education at all levels for both the prescriber and patient. The prevention of intentional misuse or abuse may require regulatory intervention.Its extended-release formulation, it is best used in patients with stable and predictable opioid requirements.

Keywords: Transdermal, Pharmacology, Toxicology, Adverse effect, Misuse, Forensic toxicology

Introduction

Transdermal system providing continuous systemic delivery of fentanyl, a potent opioid analgesic, used for managing moderate to severe chronic pain.[1]It has two drug release modes: tank system and matrix system, enabling stable and sustained release of the active ingredient, which is ideal for the relief of chronic pain. Its soluble nature enables a wide distribution in different body compartments, in particular the blood-brain barrier.[2]When administered transdermally, the bioavailability is excellent (92%).[3]

Pain affects all people. Pain may be acute (e.g., injury), episodic (e.g., headaches), or chronic (e.g., sciatic pain); regardless of its nature it decreases a patient's quality of life.[4]Fentanyl is a

synthetic opioid receptor agonist. Due to its low molecular weight, highly lipid-solubility, and good skin absorption effects,[5,6,7]fentanyl is suitable to use transdermally as a patch. Advantages of transdermal fentanyl patch include its ease of use, and its blood concentrations remain high and only drop to 50% after 16 h, when the patch was removed. Recently, it has been used for the treatment of cancer pain.[8]However, some published studies have reported that transdermal fentanyl patch induces potentially serious side-effects, such as skin irritation, and respiratory depression due to the long duration of blood concentration additionally.[9]

The average worker suffering a disorder associated with pain loses 4 days of work every month compared to a half day for a worker without a pain syndrome. Thus, in addition to improving quality of life, adequate pain control could result in billions of dollars of saved productivity.[4]This article reviews the pharmacology and toxicology of transdermal fentanyl, one of the cornerstone pharmacotherapies for patients with chronic pain.

Background

The use of transdermal fentanyl delivery systems has increased over recent years especially in patients with chronic pain who are already treated with high doses of morphine or it is derivate. Fentanyl patches, which provide steady-state fentanyl concentrations for 72 hours, are an attractive alternative treatment compared to multiple daily oral medications especially in geriatric and cancer patients. However, a large misuse potential with fatal outcomes has been described.[10-13]The minority of incidents occur in places with controlled and documented patch administrations such as hospitals or retirement centers. On the contrary, no control exits in a residential setting.[10]

Adverse events of transdermal fentanyl

Sales of Johnson & Johnson's (Janssen) Duragesic transdermal devices have steadily increased since its introduction, and had sur-passed 4 million prescriptions and nearly 2 billion dollars in 2004, though sales have fallen with the introduction of generics. Not surprisingly, there has been a concomitant increase in adverse events and emergency department (ED) visits related to the transdermal fentanyl device.[14,15] The reasons for this are unclear and likely multifactorial. In 2004, the Drug Abuse Warning Network (DAWN), a national surveillance database, reported over 8,000 ED visits in the United States due to the misuse of transdermal fentanyl.[4]

Although individual case reports confirm the abuse of fentanyl derived from the transdermal delivery system, epidemiological links are less clear. Fentanyl use data is collected by various groups including the Drug Enforcement Administration (DEA), DAWN, and medical examiners.[4]Although the latter data are fatality related, they often inadequately distinguish between misuse and abuse, and generally fail to specify the form and/or route by which fentanyl was utilized. A more obvious association from the medical examiner literature is the utilization of the transdermal fentanyl delivery systems as a method of suicide.[16]While in many cases the cause of death may be confirmed objectively, deciphering the manner of death to deter-mine who died from fentanyl abuse rather than suicide is often difficult. This decision is largely based on scene investigation, available clinical history and findings, and postmortem determinations, including analytical toxicology testing. However, even determining that fentanyl is the cause of death on the basis of postmortem blood

fentanyl concentrations is occasionally fraught with difficulty. For example, as discussed later, pharmacodynamic effects, such as opioid tolerance, and pharmacokinetic effects, such as postmortem redistribution, complicate the interpretation of the postmortem blood concentration.[4]

Clinical pharmacology of transdermal fentanyl patches

Fentanyl possesses many of the physicochemical properties essential for transdermal use.[4]The molecular weight of fentanyl base is 337 Da[17] within the maximum molecular weight con-sidered suitable for skin permeation (< 1000 Da). Fentanyl, un-like morphine and other opioids, is highly potent, and produces desired clinical effects following the systemic absorption of a fraction of a milligram in nontolerant individuals. It is typically considered that drug administration by this route is limited to drugs that are effective at doses of <2 mg daily.[4]

Additionally, fentanyl is sufficiently soluble in both the lipid and aqueous compartments of the skin to allow penetration. In its alkaloid (base) form, fentanyl readily enters the keratinaceous stratum corneum. This layer of the epidermis provides the greatest barrier to the movement of water both into and out of the body.[4]Only substances with sufficient lipid solubility can dissolve and diffuse past the ceramides and other waxy lipids of this dermal layer. Subsequent movement of drug from the lipid layer into the aqueous dermis is required to enable systemic absorption. Thus a chemical must be soluble in both lipid and water to be internalized effectively following dermal application. The relationship between the lipid and water solubility of a chemical is numerically demonstrated by its octanolwater partition coefficient. This is expressed as the concentration ratio of a chemical in octanol and in water while at equilibrium at a given temperature. Fentanyl base has an octanolwater partition coefficient of 860 (fentanyl citrate is 717 at pH 7.4), thus passes through the lipid portion of the epidermis with relative ease. Although fentanyl base and salt (citrate) are similarly bioavailable, the systemic absorption of the base appears to be slightly faster.[4] In comparison, morphine is not very lipophilic and possesses an octanolwater partition coefficient of 0.7, and predictably demonstrates poor epidermal permeability.[4]

The high lipophilicity of fentanyl results in a rapid diffusion into the lipophilic epidermal tissue with subsequent slow movement into the water-rich dermal tissue. This results in the formation of a depot in the keratinaceous layer of the epidermis. This depot formation accounts for the slow onset and prolonged effects of transdermally-delivered fentanyl. Transdermal device application sites are typically rotated in part to prevent serum con-centration fluctuations resulting from the development of large depots following consecutive use of the same site.[4]

Other dermal variables affect the rate of transdermal fentanyl absorption. Variations in skin thickness and degree of keratinization will alter its systemic bioavailability and account for much of the great interindividual variability observed with transdermal fentanyl absorption[18] which there is a wide range around the mean serum fentanyl concentration in transdermal fentanyl users. The average skin thickness of the human body is 40 μm, but ranges between 20 and 80 μm based on location, race, age, and gender, among other factors. In skin samples from 8 individuals, there was a >50% difference in the permeability of fentanyl.[19] Skin surface areas with similar stratum corneum thickness typically possess similar diffusion rates within an

individual, explaining why the chest, extremities, and abdomen are acceptable sites for transdermal device application without the need for any dosage changes.[18,19]

Following application of a transdermal fentanyl device to bro-ken skin, blood fentanyl concentrations can rise 5-fold.[4] Ex-posed tissue lacking a stratum corneum, such as mucosa, has a >30-fold increase in fentanyl absorption, and more predictable pharmacokinetics.[4] This effect permits the successful use of fentanyl citrate lozenges (Actiq) or buccal tablets (Fentora) for sedation and short-term analgesia, while explaining the potential for morbidity and mortality associated with improper use.[4] Correspondingly, fatal overdose may result from buccal mucosal application of transdermal fentanyl devices.[20]

Skin temperature elevation enhances the absorption of transdermally-applied fentanyl, perhaps either as a result of cutaneous vasodilation or of enhanced solubility of fentanyl.[21] An in-crease in skin temperature from 32°C to 40°C leads to a gradual 10- to 15-fold increase in cutaneous blood flow.[4] A 3°C in-crease in body temperature raises the peak fentanyl blood concentration by 25%.[4] Case reports detail that elevation in skin or ambient temperatures from external sources such as hot tubs or heating blankets may lead to fentanyl overdose.[4] Although blood fentanyl concentrations are often not provided in case reports, a controlled study using a 25 μg/hour transdermal fentanyl device showed that the concentration rose rapidly when the transdermal device on the skin was heated to 42°C.[4] Application of an overlay to hold in place a nonstickingtransder-mal device may be associated with altered fentanyl absorption, and raises the potential for toxicity.[22] Further study is essential to determine whether exercise produces dramatic increases in the rate and extent of transdermal absorption, as is demonstrated for the ultrapotent fentanyl analog sufentanil.[4]

Intravenously administered fentanyl has a half-life of 2–4 hours but a short duration of action of approximately 15 minutes, due primarily to redistribution.[4] Extensive firstpass hepatic metabolism limits its oral bioavailability.[4] Based on the data provided in the transmucosal fentanyl labeling (Actiq), about 50% of transmucosal fentanyl is absorbed, with half of this absorbed transmucosally and 25% escaping firstpass elimination after swallowing [59]. Bypassing the liver explains why the bioavailability of transdermal fentanyl is excellent (~92%), which has both advantages and potential liabilities.[4] Once absorbed, fentanyl, like other lipophilic compounds, achieves a large volume of distribution (6 L/kg [range 3–8]).[4] Fentanyl is a pure mu-opioid receptor agonist that demonstrates approximately 75–100 times the potency of morphine. Its high lipophilicity allows it to readily cross the blood-brain bar-rier to produce analgesia and sedation. Alterations in blood pH may affect the distribution of fentanyl between plasma and the central nervous system (CNS).[4]

Metabolism occurs primarily via oxidative dealkylation by hepatic CYP 3A4 to norfentanyl and other less active or inactive metabolites through an oxidative N-dealkylation process. The concomitant use of fentanyl with cytochrome CYP 3A4 inhibitors (e.g., ketoconazole, ritonavir, nefazodone) may result in an increase in both plasma fentanyl concentrations and the risk of adverse drug effects.[4] A small amount (8%) of fentanyl is eliminated unchanged in the urine.[4]

Comparison of transdermal delivery systems

In addition to more than 100 drugs formulated as creams and ointments, there are now 19 drugs or drug combinations administered using FDA-approved transdermal delivery systems. Most of these first-generation delivery systems rely primarily on appropriate drug properties that permit absorption into the skin without significant skin permeation enhancement. However, advances in the field through second- and third-generation transdermal delivery systems are opening the door to transdermal administration of hydrophilic molecules, macromolecules and vaccines.[23]

Most enhancement approaches increase skin permeability without providing an added driving force for transdermal transport. Chemical enhancers are an exception, because they can disrupt stratum corneum structure as well as increase drug solubility and thereby increase the drug concentration-gradient driving force. Microneedles are another exception, because they not only pierce the skin, but can carry drug into the skin via coating and encapsulation using solid microneedles or infusion through hollow needles. Although electrical methods of delivery can affect skin permeability as well as provide an electrical driving force, iontophoresis acts primarily to drive drugs into the skin and electroporation acts largely to disrupt stratum corneum structure. Because iontophoresis provides a transport driving force, it may be especially useful when coupled with another method that increases skin permeability. Such combined enhancement strategies have received previous attention in the literature.[24]

Successful transdermal delivery is based on achieving a suitable balance between effective delivery and safety to the skin. Some of the third-generation systems rely on the hypothesis that relatively large, micron-scale defects in the stratum corneum should be well tolerated by patients as long as significant damage is not done to living cells in the viable epidermis and dermis. Reports to date suggest that this hypothesis is reasonable, based on data from a growing collection of clinical trials that have advanced through phase 1 safety trials and into phase 2 and 3 studies of efficacy, especially using microneedles and thermal ablation. This may not be surprising, given that the skin reliably repairs itself without scarring or infection after being routinely subjected to microscopic defects caused by scrapes, scratches, shaving, hypodermic injection, and other minor mechanical trauma.[23]

Clinical impact relies not only on a transdermal delivery system that administers drugs in a safe and effective manner, but one that is also low-cost and easy to use, given that most transdermal delivery systems are designed for self-administration at home. The various chemical enhancers can be integrated into small, inexpensive patches that patients find convenient. The various physical enhancers may be more effective to deliver macromolecules and vaccines, but are generally driven by hand-held devices that require electrical power. As a result, most physical enhancers rely on relatively costly, re-usable devices that interface with a disposable drug reservoir component. Microneedles are an exception, because they can deliver macromolecules and vaccines, should be inexpensive to manufacture as single-use patches, and do not require a power supply. However, microneedles are also unique in that they are physically invasive, which raises additional safety and sterility considerations.[23]

Pharmacokinetics of the transdermal fentanyl device

Fentanyl becomes detectable in the serum within 1–2 hours of application of a transdermal fentanyl device. However, thera-peutic serum fentanyl concentrations are not achieved until ap-proximately 12–16 hours after transdermal device application.[4] The mean time to maximal serum concentrations (Cmax) averages about 36 hours, regardless of the transdermal device strength, but there is substantial intersubject variability (17–48 hours).[4] The Cmax achieved, which depends on the "strength" of the transdermal device, ranges from 0.3 ng/mL for a 12.5 μg/hour transdermal device to 2.6 ng/mL for a 100 μg/hour transdermal device.[4] For reference, an IV bolus of 2 g/kg produces a peak serum concentration of 11 ng/mL.[4] In com-parison, an effective postoperative analgesic serum concentration is 0.3–0.7 ng/mL.[4] These concentrations are substantially higher than those tolerated by an opioid naïve patient, demon-strating the development of opioid tolerance with continued use. The apparent half-life of fentanyl delivered by a transdermal de-vice (following its removal) approaches 17 hours (16–22 hours) due to continued absorption from the stratum corneum depot during the elimination phase.[4] Based on clinical studies and those with human epidermal cells, dermal metabolism is considered inconsequential.[4]

Table: Physical and Pharmacokinetic Characteristics of the Transdermal Fentanyl Device[4]

Transdermal device strength	Transdermal device surface area (cm2)	Fentanyl content (mg)	Mean(SD) time to maximal concentration	Mean (SD) maximal plasma concentration (ng/mL)
12.5 μg/h	5	1.25	27.5(9.6)	0.3(0.2)
25 μg/h	10	2.5	38.1(18.0)	0.6(0.3)
50 μg/h	20	5	34.8(15.4)	1.4(0.5)
75 μg/h	30	7.5	33.5(14.5)	1.7(0.7)
100 μg/h	40	10	36.8(15.7)	2.5(1.2)

One of the advantages of this form of fentanyl delivery is ex-emplified by the relatively smooth pharmacokinetic curve of blood fentanyl concentrations that is produced by transdermal device delivery, particularly when compared to intermittent dosing by virtually any other route. Mean curve of serum fentanyl concentration is relatively flat over the 3-day period following reaching steady state, without the peaks and troughs typical of intermittent dosing. There is a somewhat wide range between the minimum and maximum serum concentrations attained, highlighting the importance of close observation during the initiation of this therapy. Elderly patients have a slightly longer time to peak concentration and a prolonged half-life following removal of the transdermal device.[4] In 1.5- to 5-year-old patients, the fentanyl plasma concen-trations were approximately twice as high as that of adult patients.[4] In older pediatric patients, the pharmacokinetic parameters were similar to that of adults. A review of the use of the reservoir transdermal device in children undergoing treatment for cancer-related pain suggests that individual pharmacokinetics parameters of transdermal fentanyl seem to differ from adults (e.g., longer time to reach steady-state serum concentrations, higher weight-based clearance), safety concerns remain, and there is a significant need for additional information.[4]

Clinical effects

The clinical effects of fentanyl, regardless of route of administra-tion, are similar to those of other opioids, and are similarly de-pendent on both the dose and the degree of patient tolerance. At serum fentanyl concentrations of 0.63–1.5 ng/mL, postoperative analgesia is produced in

most opioid-naïve patients. Hypoventilation begins to manifest at concentrations >1.5 ng/mL, a subtherapeutic serum concentration for some.[4]

With escalating doses, analgesia is preserved and mild sedation is noted. Patients in this state are easily arousable with physical stimulation. As concentrations increase further, deep sedation develops, requiring greater stimulation, and the arousal period shortens. Further increasing fentanyl concentrations produces coma, with the inability to arouse the patient. Respiratory depres-sion essentially parallels sedation and analgesia, with the eventual development of apnea. Simultaneous loss of protective airway reflexes highlights the requirement for advanced ventilatory management skills. Serum fentanyl concentrations of 3.0 ng/mL typically produce these latter effects in opioid-naïve patients.[4]

Miosis is a common side effect and may be used diagnostically to identify both compliance and overdose. Gastrointestinal effects, dyspnea, and pruritis can be discomforting.[25]The rigid chest syndrome associated with fentanyl infusion is not well described with the transdermal fentanyl device. This may be related to the slower rate of rise of the serum levels with transdermal fentanyl devices than with IV infusion.[4] Mydriasis, vomiting and diarrhea, and piloerection may be used to identify opioid withdrawal.[4]

Intentional transdermal fentanyl device misuse and abuse

Fentanyl is reportedly commonly abused by healthcare professionals[4] and its analogues have been implicated in several large epidemics of “heroin” poisoning.[4] Fentanyl abusers note that it produces euphoric effects that are similar to heroin.[4] Transdermal fentanyl devices are suitable for abuse in several ways. The fluid state of the drug reservoir layer allows fentanyl to be extracted. Every transdermal device, even after being used, contains a significant quantity of fentanyl. Even the smallest-dose transdermal device contains 1.25 mg (or 1250 μg) of fentanyl. This is 10–20 times the typical initial IV therapeutic dose of 50–100 μg [1 μg/kg] used during procedural analgesia and sedation. Many of the fatalities reported from abuse of the transdermal fentanyl device are associated with IV admin-istration of the fentanyl-containing gel extracted from the reservoir transdermal device.[26,27] One interesting report based on information from a street user suggests that the matrix transdermal device is preferred over the reservoir transdermal de-vice by Canadian opioid abusers.[4] By cutting the matrix trans-dermal device into the desired size, users can place the fragment in their mouth, allowing rapid transmucosal absorption.[4] Fentanyl may also be eluted from the transdermal device using sol-vents and then injected.[4]

Other reported routes of abuse include inhalation of a pyrolyzed transdermal device, insertion of a transdermal device rectally, and drinking water in which a transdermal fentanyl device was steeped as a tea bag.[4] Despite its poor oral bioavailability, ingestion of fentanyl gel may result in poisoning and death.[28,29] It remains unclear to what extent trans-dermal device ingestion–related fatalities are due to sublingual, transmucosal, or gastrointestinal absorption, or a combination thereof. Fentanyl in other formulations intended for transmucosal absorption (e.g., Fentora, Actiq) has resulted in fentanyl morbidity and mortality.[4] Even accounting for fentanyl’s poor enteral bioavailability, each transdermal device contains a sufficient amount of fentanyl to be lethal.[4]

Previously-worn transdermal devices may contain 28–84% of the initial drug [102].

Transdermal fentanyl devices have been reportedly removed from decedents and nursing home patients for subsequent abuse,[4] prompting healthcare facilities to develop policies for their safe disposal. Exposure to discarded or misplaced transdermal devices has also proven consequential.[28]The manufacturers and FDA have gone to substantial lengths to educate patients (e.g., fold the sticky side together and flush down a toilet) and provide safe mechanisms for transdermal device use and disposal, largely to prevent unintentional childhood exposure to discarded transdermal devices.[30]

Transdermal device leak

Concerns for dysfunction of the TTS polyester backing with subsequent fentanyl poisoning following gel leakage onto intact skin prompted the manufacturers to issue an "urgent product recall" in 2004 of more than 2 million transdermal devices.[31] They noted the possibility that "a small percentage of these trans-dermal devices which were distributed in the U.S. may leak medication along one edge" due to a "fold over defect" of the backing material, which occurred during the manufacturing process. The company estimated that <19,000 transdermal devices out of a lot total of 440,000 (~5%) were potentially defective.[4] Reservoir leak-age during clinical use could cause the fentanyl-containing gel to spread over the skin, increasing the surface area for absorption and also accelerating the evaporation of the alcohol and water solvents of the gel. Currently undefined, this evaporative process may speed or slow the delivery of fentanyl across the epidermis. Although improved manufacturing practices and strict quality assurance procedures were implemented by the manufacturers.[32]

Relevant forensic toxicology

The most consistent pathological finding on postmortem examination is pulmonary edema,[4] and as with other opioid fatalities, such as heroin or methadone, the nonspecific pathology findings require that the determination of the cause of death await the toxicological analysis. In many of the transdermal fentanyl fatality reports the clinical exposures are inadequately detailed (or not readily discernable), which may increase the complexity of the cause of death determination. Additionally, many of these reports involve concomitant exposures to other substances in often undefined concentrations, hampering the ability to fully appreciate the role of fentanyl. Because of the lack of structural similarity, fentanyl should not be expected to pro-duce a positive result on the opioid/opiate component of a standard immunoassay-based "urine drug screen".[4] Liquid chromatography-mass spectrometry is the established standard for measuring serum fentanyl concentrations.[33]

In a large series of fatalities from fentanyl abuse (not trans-dermal device–related), the mean postmortem blood concentration was 3 ng/mL.[4] Another similar series reported a range in serum concentration of 5–120 ng/mL, with a median of 22 ng/mL, in 19 fatalities deemed to be due to drug overdose, though not necessarily abuse related.[4] Several of the deaths were associated with transdermal fentanyl delivery systems; one patient on a transdermal fentanyl dose of 300 μg/hour had a post-mortem blood fentanyl concentration of 120 ng/mL.

The mean measured fentanyl blood concentration in 6 trans-dermal fentanyl fatalities was 21 ng/mL (10–38 ng/mL).[4] In a series of 25 deaths potentially involving transdermal fentanyl, the 8

cases felt to be “clearly not related” had heart blood concentrations of <2–7 ng/mL, while in the 12 cases considered at-tributable solely to fentanyl the heart blood concentrations ranged from 16 to 139 ng/mL.[34] Postmortem redistribution is considered to be minor, though variable, with a heart/femoral ratio of 1.6 (range 0.7–4.6) noted in a study of 13 transdermal fentanyl device–related fatalities.[4]

Although it would not be surprising that transdermal fentanyl device injection abuse would result in higher blood concentrations than with transdermal use, in one study of 23 transdermal fentanyl device–related deaths, the fatalities associated with a transdermal route of poisoning had higher mean blood fentanyl concentrations (21 ng/mL) than those with an IV route (7 ng/mL).[4]

Following oral ingestion of a used 25 μg/hour transdermal fentanyl delivery system, a 1-year-old girl had the following fentanyl and norfentanyl concentrations: peripheral blood, 5.6 and 5.9 ng/mL; heart blood, 19.0 and 8.9 ng/mL; and liver, 235 and 26 ng/g.[28] This suggests that although first-pass hepatic metabolism is substantial, poisoning following transdermal device ingestion remains a concern.[4]

Management of fentanyl poisoning

The management of fentanyl poisoning, whether transdermal or another route, should focus on ventilatory support and oxygenation first and foremost. This is most typically provided by bag-valve-mask ventilation, although endotracheal intubation or other measures may be needed in some patients. Although naloxone effectively antagonizes fentanyl at the muopioid receptor and may avoid intubation in many, it may be avoided best in mildly-poisoned, nonvomiting, opioidtolerant patients with adequate spontaneous ventilation. Patients provided solely supportive care will not awaken immediately, which may not prove satisfactory to the clinical staff. However, administration of naloxone in conventional (0.4–2 mg) dose to this latter group of patients is associated with fulminant awakening and precipitated opioid withdrawal, with its attendant complications.[4] In addition, recrudescence of an underlying pain syndrome, if present, may be undesirable. Judicious titration, starting at very low doses (e.g., 0.05 mg IV), while providing ventilatory support and oxygenation, may provide a more gradual, and safer, awakening. Failure to arouse with an appropriately-titrated dose of naloxone may signal the presence of an overlooked diagnosis, such as a concomitant exposure or cerebral hypoxia. Due to the high potency of fentanyl, higher-than-conventional doses of naloxone may be required on rare occasions.[4]

Although the transdermal fentanyl device should be immediately removed, this is inadequate monotherapy as the reservoir of fentanyl in the stratum corneum will continue to deliver fentanyl systemically for several hours.[4]Although the skin should be cleansed to remove any external drug, the rapidity of absorption makes the benefit of this questionable. Additionally, cleansing would likely have limited or no effect on removing intradermal fentanyl. The optimal cleansing compound is undefined, and soap and water are likely acceptable. It would be appropriate to completely examine the patient for the presence of an unsuspected transdermal fentanyl device.[4]

Related previous work

Nelson et al.[4]Fentanyl is a high-potency opioid that has many uses in the treatment of both acute and chronic pain. Intentional or unintentional misuse, as well as abuse, may lead to significant clinical consequences, including death. Both the US Food and Drug Administration (FDA) and Health Canada have warned of potential pitfalls associated with transdermal fentanyl, although these have not been completely effective in preventing life-threatening adverse events and fatalities related to its inappropriate use.[4]

Andresen et al. reported Fentanyl is potent, highly lipid soluble, rapidly acting μ-opioid receptor full agonist. This means that it may have ceiling effect and demonstrate both agonist and antagonist effects. The primary side effects of buprenorphine are similar to fentanyl (e.g. nausea, vomiting, and constipation), but the intensity of these side effects is reduced significantly compared to full agonist, fentanyl. The most severe and serious adverse reaction associated with opioid use is respiratory depression, the mechanism is behind fatal overdose. The pharmacology profile of buprenorphine is complex but unique, and contributes to its distinct safety and efficacy when it is used under appropriate clinical indications.[34]

Conclusion

This review was to provide transdermal (TD)Fentanyl is an extremely potent opioid carrying significant analgesic benefi and efficacy in patients with pain. Further-more, transdermal administration of fentanyl extends many of the drug's therapeutic benefits, but also adds unique factors that may complicate the drug's safety. There are many reasons for the enhanced toxicity, including inappropriate prescription and improper use. As a potent opioid analgesic in a concentrated transdermal device system, its abuse potential is extremely high and carries a high risk of morbidity or mortality. Physician education and awareness concerning the numerous and often re-sourceful ways with which transdermal fentanyl may be misused or abused hopefully will result in fewer poor outcomes and ultimately save lives.Further studies directly transdermal (TD) fentanyl in pain would be useful; long-term data, in particular, are lacking.

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