Review Article on - Fentanyl transdermal patch: The silent new killer

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***Abstract*: Fentanyl is a synthetic opioid that is used as a narcotic analgesic supplement in general and regional anaesthesia, as well as in the treatment of chronic pain that is persistent and severe. Transdermal fentanyl patches are a great alternative for treating chronic and cancer-related pain, but they can be fatal if used incorrectly or abused too much. Overdose deaths from novel synthetic opioids have been on the rise globally as a result of fentanyl adulteration in the illegal drug supply.**

***Keywords:* Fentanyl, Synthetic Opioids, Transdermal Fentanyl Patches, Abuse**

1 Introduction:

In the late 1950s, the Belgian company Janssen Pharmaceutica created fentanyl (N-1-(2-phenylethyl)-4-piperidinyl-N-phenyl-propamide) in the search for effective, rapid-acting analgesics with great potency. Fentanyl (N-1-(2-phenylethyl)-4-piperidinyl-N-phenyl-propamide) is a synthetic opioid that is 50–100 times more potent than morphine. It is used in general and regional anaesthesia, neuroleptanalgesia (in combination with the neuroleptic droperidol), and the management of persistent moderate to severe chronic pain that requires continuous transdermal opioid administration for an extended period of time and cannot be controlled Fentanyl was recently the subject of a review. In contrast to the majority of opiate deaths in prior decades, a recent assessment of fentanyl and non-pharmaceutical fentanyl highlighted the fast nature of many deaths following fentanyl usage. The most commonly seized synthetic opioids include fentanyl, furanyl fentanyl, acetyl fentanyl, and U-47700.3. Abuse of fentanyl has been widely documented in the literature. More than 63.600 drug overdose deaths were reported in the United States in 2016, and the so-called "synthetic opioid crisis" was declared in Europe in recent years. Because fentanyl is highly lipophilic, it quickly penetrates the central nervous system. Fentanyl has a half-life of 3 to 12 hours, and it is extensively metabolised, largely to norfentanyl, primarily by cytochrome P450 CYP3A4.

2 Materials and methods:

A literature search was conducted using the National Centre for Biotechnology Information's database, followed by a critical evaluation of the studies found. In the title, abstract, and keywords, the search terms were "Fentanyl," "Patch," and "Death." Only the abstracts of 63 articles linked to fatalities utilising fentanyl transdermal patches were chosen for further research. Only 23 of them met our criteria.

The references of the chosen articles were personally checked, and we discovered 6 additional publications that fit our interests. In our research, we looked at a variety of studies. Finally, this analysis includes 29 articles: 20 case reports or case series, 8 retrospective investigations, and 1 review (each case described in this review had already been considered in the other articles). This review comprises articles from all over the world, spanning a 26-year period.

3 Pharmacology of fentanyl:

Fentanyl's pharmacological effects are mediated through activation of the mu opioid receptor (MOR), which has a poor affinity for the delta and kappa opioid receptors. In addition to analgesia and anaesthesia, the substance causes drowsiness, relaxation, and euphoria, the latter being less apparent than with heroin and morphine, sedation, weariness, disorientation, anxiety, hallucinations, and respiratory depression, as do other opioids. Furthermore, fentanyl crosses the blood-brain barrier quickly, resulting in increased analgesic effectiveness, as evidenced by a half-life of 5 minutes for plasma and cerebrospinal fluid equilibrium. Thus, binding affinity or half-life have no bearing on fentanyl's enhanced analgesic effectiveness and speedier onset when compared to morphine. Fentanyl levels drop quickly when it is redistributed to different tissues, and it is quickly sequestered in body fat, contributing to its brief duration of action.

4 Absorption:

Fentanyl's lipophilic characteristics allow 46–66% of the given dose to be absorbed into dermal tissue, although absorption into water-rich tissues is slower. The outcome is the creation of a depot in the epidermidis' keratinaceous layer, which has a gradual onset and long-lasting effects following delivery. Because of its great solubility in fat and water, as well as its low molecular weight, fentanyl can be delivered trans dermally. Patches with distribution rates of 25, 50, 75, and 100 g/h are currently available. Fentanyl distribution appears to be unaffected by local blood flow or anatomical site of administration. However, raising the body temperature to 40°C can boost absorption by about a third. Interindividual diversity exists in the pharmacokinetics of transdermal fentanyl. In surgical patients, an average bioavailability of 92 percent has been determined after transdermal administration. Transdermal fentanyl absorption, on the other hand, can be affected by a variety of factors, including skin thickness, temperature, injury or inflammation, depilation, cosmetic procedures, and the degree of keratinization. The amount of blood flow through the skin where the patch is put can also affect the pace of medicine absorption.

5 Metabolism and elimination:
Fentanyl is metabolised primarily by cytochrome P450 (CYP) 3A4. Norfentanyl is the primary metabolite, with lesser metabolites such as despropionylfentanyl, hydroxy fentanyl, and hydroxynorfentanyl showing no clinically significant pharmacological activity. The inactive metabolites, as well as less than 10% of the intact molecule, are eliminated primarily in urine and faeces.

6 Clinical features:
This drug is used to treat chronic pain that is severe (such as due to cancer). Fentanyl belongs to the opioid analgesics class of medicines. It alters the way your body perceives and responds to pain by acting on the brain. Fentanyl patches should not be used to treat pain that is minimal or will go away in a few days. This drug should not be used on a "as required" basis. It is possible to have nausea, vomiting, constipation, light headedness, dizziness, drowsiness, or headache. Mild irritation, itching, or redness may occur at the application site. Coma, lethargy, respiratory depression, and arrest are the most typical overdose symptoms. A recent analysis of fentanyl and non-pharmaceutical fentanyl found that many deaths from fentanyl usage occur quickly, in contrast to the majority of opiate deaths.

7 Epidemiology:
Overdosing on fentanyl patches and abusing them is a global problem. A total of 674 fatal fentanyl patch overdose cases were investigated. The treatment of a fentanyl overdose is dependent on the patient's clinical condition and the circumstances. Sex distribution was available in 26 of the 29 articles, with males (68%) having a higher prevalence than females (32%) [. In 25 of the 29 studies, age distribution was given, with a range of 1 to 95 years and death rates for the 31–40 and 41–50 decades. Initial care should focus on protecting the airway and maintaining breathing and circulation in both community settings and hospitals. Initially, a 0.4 mg intravenous or 0.8 mg intramuscular naloxone dose is given, followed by increasing doses every 2-3 minutes until clinical response is apparent or an ambulance arrives.

8 Way of administration:
Fentanyl was the first opioid used to relieve pain through a transdermal method. Fentanyl patches release 12.5, 25, 50, 75, and 100 g/h. On flat areas of the thoracic cage and/or upper arm, a patch should be put in the region of intact, non–irradiated skin. Due to a layer of sweat separating the active surface of a patch from the skin in individuals with fever and high sweat, medication absorption may be disrupted. The onset of the analgesic activity of the fentanyl patch can take up to 12 hours after it is first administered. Due to a sluggish onset of analgesic activity after the initial patch application, fentanyl in patches is not advised for the treatment of acute postoperative pain.

9 Manner and cause of death:
The manner and cause of death were investigated in 27 of the 29 publications. Drug misuse was the cause of death in 63.5 percent of the cases. Fentanyl was accidentally administered in 93 cases (16.2 percent) due to the overuse of a transdermal patch. In fatal situations, the misuse is not limited to the route of administration of patch-stored fentanyl. In 645 deaths, the route of administration of fentanyl was reported. Intravenous (n = 455, 70.5 percent) was the most common method of administration, followed by transdermal fentanyl patches (n = 148, 23.0 percent). Oral/transmucosal (n = 29, 4.5 percent), oral and transdermal usage concurrently (n = 6, 1 percent), ingestion (n = 4 1 percent), transdermal and intravenous route simultaneously (n = 2, 1 percent), and inhalation (n = 1, 1 percent) were among the less prevalent modes of administration described.

10 Associated drugs:
In 18 of the 29 papers, other medications were used in conjunction with fentanyl. The most common drugs coupled with fentanyl were opioids and antidepressants, followed by benzodiazepines, ethanol, cocaine, and methamphetamine. When Fentanyl is coupled with 1,2-Benzodiazepine, the risk or severity of undesirable effects can be raised. When Fentanyl is coupled with aceclofenac, the risk or severity of hypertension can be enhanced.

Conclusions:
A summary of fatalities associated with the therapeutic and nontherapeutic use of fentanyl transdermal patches, toxicity mechanisms, and clinical signs. Fentanyl transdermal patch misuse and abuse is a severe problem in a number of nations throughout the world. Males (68%) are more likely than females (32%) to die from fentanyl overdose, with a wide range of ages among users**.**

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