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Oral and buccal abuse of transdermal opioids : an underdetected but potentially lethal practice

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Abstract : *Objectives :* Transdermal opioid patches (TOPs) are effective and well tolerated in patients with moderate to severe chronic pain syndromes. Their specific pharmacological properties, however, make them prone to abuse. The objective of this article is to describe the practice of oral and buccal abuse of TOPs and to discuss its clinical implications.
Methods : We present the case of a patient admitted to the intensive care unit after oral abuse of transdermal opioid patches. Additionally, a narrative literature review on the topic is conducted, referring to Pubmed and Embase.
Results : Oral or buccal TOP abuse is the most frequent method of TOP abuse, followed by intravenous injection, inhaling, and applying multiple patches. The main reasons for TOP abuse include drug addiction, suicidal behavior and self-medication. Oral ingestion is potentially lethal because of the high doses of fentanyl that are found in a single patch. Buccal abuse results in fast elevations of fentanyl serum concentrations, caused by transmucosal absorption of fentanyl, thus bypassing hepatic metabolism. During emergency management, naloxone should be administered in a continuous infusion, given the high risk of recurrence of symptoms. Evidence suggests that transdermal buprenorphine is safer in terms of abuse potential. This is explained by its ceiling effect for respiratory depression and its lower peak effects in supratherapeutic doses. Risk factors for abuse include history of substance use disorder, prior opioid overdose and mental illness. Patients with suspected opioid abuse should be referred to pain clinics, mental health specialists or drug addiction facilities.
Conclusion : Oral or buccal abuse is the most reported non-dermal form of TOP abuse. When ingested or chewed, TOPs pose considerable health risks. It is critical to screen patients with chronic opioid therapy regularly for opioid use disorder. When confronted with patients at risk of abuse, close monitoring and referral to specialist care is advised.

Keywords : transdermal ; opioid ; buccal ; oral ; abuse.

Introduction

Even though problematic opioid use has gained a lot of attention during the last two decades, a recent study by the OECD (Organisation for Economic Co-operation and Development) showed that opioid-related deaths in developed countries have further increased by 20 % between 2011 and 2016 (1). The introduction of transdermal opioid patches (TOPs) has been associated with increases in highly potent opioid consumption and opioid-related death in Europe (2-4). Moreover, transdermal patches have been found to be the main source of legal fentanyl diversion by drug users (5).

Transdermal opioid patches are registered for the treatment of chronic malignant and non-malignant pain. Currently, TOPs contain either buprenorphine or fentanyl as active ingredients. Buprenorphine is a partial opioid agonist at the μ-receptor, whereas fentanyl is a synthetic full opioid agonist. Both opioids have a potency of almost 100 times that of morphine (6).

Several authors have reported on novel methods of TOP abuse (7, 8). By changing the route of administration, new toxicological complications arise. In this article, the case of a patient is presented who was admitted to the intensive care unit after chewing on two transdermal fentanyl patches

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prescribed for spondyloarthritis. Furthermore, a literature review is conducted on the epidemiology and pharmacology of oral and buccal TOP abuse. Finally, emergency management and implications for treatment are discussed.

Methods

A literature review was conducted in PubMed and Embase. The following search terms were used: 'oral abuse transdermal opioid', 'oral ingestion opioid patches', 'drug abuse AND transdermal opioid' and 'transmucosal OR buccal abuse transdermal opioids'. No limitations on publication date were used. Exclusion criteria were other routes of administration and accidental overdose. Relevant publications were selected by abstract. Reference searching was performed in key publications in order to find additional articles. Grey literature was screened for relevant guidelines, reports, information websites and presentations of professional associations (Fig. 1). Approval of the internal review board was obtained, as well as written informed consent for the case report.

Case report

A 47-year-old Caucasian male was arrested by the police after a burglary. Although he seemed intoxicated, the patient was detained in police custody for safety reasons. The next morning, the patient was found unconscious in his cell and was transferred to the emergency services of a general hospital. On arrival, the patient had a Glasgow Coma Scale of 3/15, respiratory rate of 5 breaths per minute, blood pressure of 120/80 mm Hg and glycaemia of 103 mg dL^{-1}. Pulse oximetry was 81 % and blood gas analysis showed metabolic acidosis. Serum blood analysis was normal, except for mild leucocytosis and elevated creatine kinase. The electronic medical record indicated that the patient had been prescribed fentanyl (Durogesic®) 25 µg h^{-1} patches for spondyloarthritis. Toxicological analysis was positive for ethanol (0.6 g L^{-1}), clomipramine (82 µg L^{-1}) and amphetamines, but not for opioids.

Based on the clinical signs of opioid overdose, the patient was treated with naloxone 0.1 mg IV and quickly regained consciousness. After 30 minutes, however, the patient became unresponsive again and was transferred to the intensive care unit for monitoring. Later that day the nurses found two pieces of plastic in his bed. When he awoke, the patient admitted that he had chewed on two fentanyl 25 µg h^{-1} patches that were attached to his body when he was arrested by the police. During psychiatric examination, the patient told he regularly chewed on fentanyl patches for pain relief, but also to obtain a high.

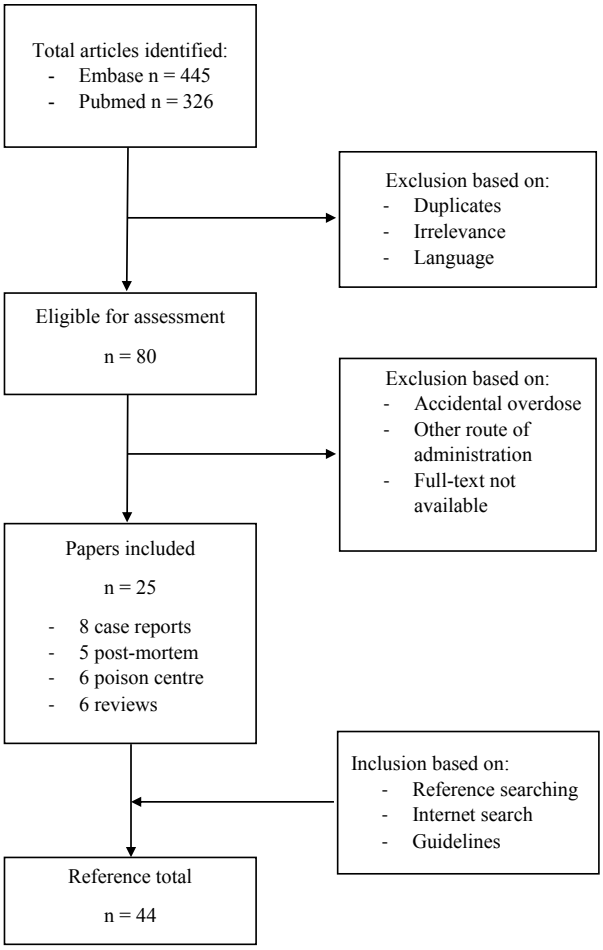

Figure 1. — Flow chart of the literature search strategy

When his medical condition stabilized, the patient could be transferred safely to the psychiatric emergency service for further observation. The following day, he experienced mild agitation and irritability, for which he was treated with oral diazepam 2x10 mg daily. No other opioid withdrawal symptoms could be observed. For his pain symptoms, paracetamol 4x1 g and tramadol ER 2x50 mg were prescribed after consultation with the pain specialist in the hospital. Three days later, the patient was referred to a specialised drug addiction facility for further treatment.

Results

Epidemiology

The use of medically prescribed opioids has increased throughout Europe (9). Some countries,

such as France and The Netherlands, have seen a nearly doubling in prescription of highly potent opioids in the past 15 years (10, 11). The prescription of fentanyl in particular increased by 39 % between 2010 and 2018 in Europe (12).

Belgium has the second highest daily use of fentanyl per capita in Europe with 12.582 defined daily doses per million (12). Data from the National Institute for Health and Disability Insurance (RIZIV) showed a 26 % increase of fentanyl prescriptions between 2010 and 2019, with a gradual stabilization after 2016 (Fig. 2).

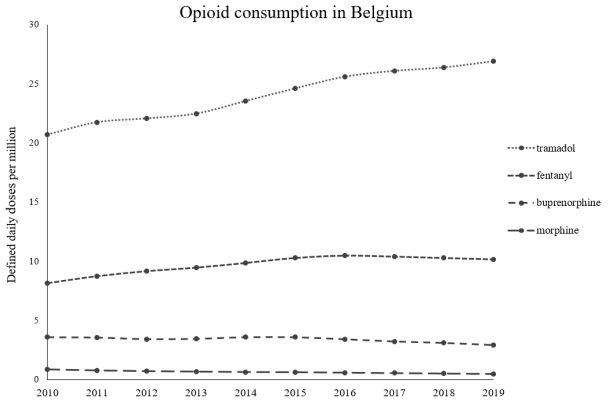

Figure 2. — Consumption of fentanyl compared to other opioid drugs in Belgium (data derived from Cel Farmanet, National Institute for Health and Disability Insurance (accessed 26/10/2020)

Schifano et al. studied adverse drug reactions associated with fentanyl, as reported to the European EudraVigilance database. They identified 559 cases, of which 185 (33 %) resulted in death and 192 (34%) in prolonged hospitalization. Although the route of administration was only infrequently reported, 23 cases of transdermal patch ingestion were noted (13). Of all cases reported to the Belgium Early Warning System on Drugs in 2017, more than 10 % were associated with fentanyl and its analogues (14).

When considering oral abuse of transdermal fentanyl patches in particular, data from poison center studies show mortality rates of 5 - 8.6 % (15-18). Drug addiction was the most frequently reported cause of oral TOP intoxication, followed by suicidal behavior and misuse for analgesic purposes. Patients were mostly male (54 %), with an average age of 42 years. The majority (74 %) obtained the patch legally via prescription (15-19).

Pharmacology

Originally, TOPs were developed in two distinct forms. In one form the drug is held in a gel

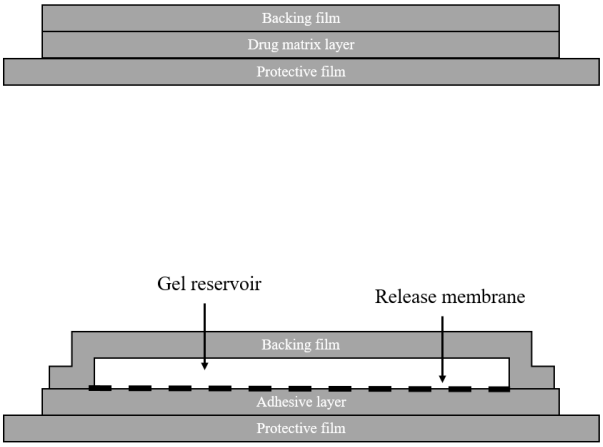

Figure 3. — Construction of the matrix patch (above) and gel reservoir patch (below) (6).

reservoir after which it is delivered to the skin by means of a rate-controlling membrane. In the other form, the active drug is slowly released from a polymer matrix layer (Fig. 3) (20).

Fentanyl is lipophilic and has a low molecular weight, making it highly suitable for transdermal use. Because transdermal delivery bypasses hepatic first-pass metabolism, bioavailability is high (92 %) (21). The mean time to maximum serum concentration via the transdermal route is 36 hours. Blood concentrations vary between 0.3 ng mL^{-1} and 2.6 ng mL^{-1}, depending on the dose. The half-life of transdermal fentanyl is approximately 17 hours after removal of the patch, due to the drug depot that has formed in the epidermal layers (6).

Oral ingestion implies swallowing either the contents of a reservoir patch, or the patch as a whole. Despite low oral bioavailability (35 %) (22), this method is nonetheless potentially lethal because of the high doses of fentanyl that are found in a single patch. In 2014, Plasencia et al. examined the release of fentanyl from an intact transdermal patch in simulated gastric and intestinal fluids. After three hours, an average of 26 % and 41 % of the total available dose was released, respectively. While this study has its limitations, the results indicate rapid onset of oral fentanyl patch toxicity (23).

In what is described as buccal or transmucosal abuse of TOPs, the opioid patch is placed in the buccal cavity and is sucked or chewed on (7). When absorbed through the buccal mucosa, the bioavailability of fentanyl increases to almost 50 % (22). Data on buccal fentanyl tablets show that about 25 % of the original dose is quickly absorbed transmucosally and released into the systemic circulation. After swallowing the remaining content, another 25 % of the total dose

remains after first-pass metabolism and becomes systemically available. The time to maximum serum concentration for transmucosal fentanyl is 20-40 minutes. The peak plasma concentration is 2.5 ng mL^{-1} after transmucosal administration of a single dose of 1600 µg (24). As a comparison, a 100 µg h^{-1} patch contains 16.800 µg of fentanyl (25).

A large individual variation exists in fentanyl concentration-effect association, mostly related to the induction of tolerance and concomitant drug use. It is generally accepted that analgesia occurs at serum concentrations between 0.63 and 1.5 ng mL^{-1}. Hypoventilation can be seen at 2.0 ng mL^{-1} (25). With fentanyl serum concentrations above 3.0 ng mL^{-1}, toxic effects such as apnea and coma can develop in opioid naïve patients (6). Fatalities involving different types of fentanyl patch abuse have been associated with post-mortem concentrations ranging from 3-383 ng mL^{-1} (26).

Routes of Administration

Several methods of opioid patch abuse are described in the literature. Originally, reports showed patients either injecting the content of fentanyl reservoir patches intravenously, or heating and inhaling the smoke of the fentanyl gel (27, 28). More recently, data from poison centers show that chewing or ingesting opioid patches has become the most reported non-dermal route of administration (39 %-50 %) (16, 19, 29). Sjoberg et al. studied 202 cases of fentanyl patch intoxications, as reported to the Swedish Poisons Information Centre. Except for chewing or ingesting TOPs (39 %), other routes of intoxication were intravenous injection (24 %), smoking of the patch (15 %), dermal application (12 %), combined application (8 %) and rectal insertion (< 1 %) (table 1) (16).

Emergency Management

Intoxication with TOPs results in the opioid toxidrome characterized by respiratory depression, decreased consciousness and bilateral miosis. Pupil size can be misleading in case of co-ingestion with mydriatic drugs. Emergency management is based on the ABC principle. The first goal is to secure the airway, paying attention to remaining patches in the trachea or bronchi, which is an additional cause of TOP mortality (30). A patient should be intubated and ventilated when spontaneous breathing is compromised. In case of cardiac arrest, resuscitation should be initiated as quickly as possible. Activated charcoal is generally only considered useful when patients present to the hospital within one hour after ingestion. Special care should go to a full body examination, removing remaining patches (31).

The gold standard treatment of opioid overdose is naloxone. Naloxone is a competitive opioid antagonist with a rapid onset of action of 2 minutes and a half-life of 60 minutes (32). The recommended starting dose in acute intoxications is 0.4-2 mg IV (33), although initial doses of 0.04 mg have also been studied with similar results (34). In case of insufficient effect, dose escalation can be performed with re-evaluation after 2 minutes (35).

However, as fentanyl is a highly potent and high-affinity opioid, single boluses of naloxone are often insufficient and symptoms of overdose can recur. This phenomenon is enhanced by the presence of hydroxyethyl cellulose in the TOP gel reservoir, a component that is biochemically inert and is also found in 'extended release' tablets. Furthermore, high doses of fentanyl can lead to saturation of metabolic enzymes, increasing the duration of effect (31). For these reasons, it is advised to give patients a continuous infusion of naloxone, instead of single boluses. As a rule of thumb, two-thirds of the dose that successfully reversed symptoms should be given hourly as a continuous infusion for approximately 10 hours (35).

Implications for treatment

The Center for Disease Control (CDC) published guidelines for prescribing opioids in chronic pain conditions. In patients receiving chronic opioid therapy, it is important to regularly

Table 1.

Methods of TOP abuse in order of magnitude (17)

Method	***Frequency***	***Practice***
Chewing and/or ingestion	39 %	Placing the patch in the buccal area to suck or chew on, swallowing the patch
Intravenous injection	24 %	Extracting the contents of a patch, mixing it with acid and injecting
Smoking/inhaling	15 %	Heating the gel content of a patch on tin foil, inhaling the smoke through a tube
Dermal application	12 %	Applying multiple patches, abrading the skin, applying heat to the patch
Other	<1 %	e.g. rectal insertion
Drinking	N/A	Placing the patch in hot water to simmer, drinking the fluid

screen for opioid abuse. The CDC identified several risk factors, including history of substance use disorder or drug overdose, and mental illness.

Behavioral components of addiction can be recognized using the 'three C's': loss of control, craving and use despite negative consequences. Examples are signs of somnolence or withdrawal, patients demanding new prescription or reporting lost medication, and decreases in social or professional functioning. Screening questionnaires such as the *Drug Abuse Screening Test* (DAST) and the online *Alcohol, Smoking and Substance Involvement Screening Test* (NM-ASSIST) can complement urine drug testing and family history for detecting concurrent substance abuse (36).

When opioid use disorder is suspected, clinicians should discuss this openly with their patient. Treatment options should be presented, including drug tapering in combination with non-opioid treatment strategies, cognitive-behavioral therapy or referral to the pain clinic (37).

Discussion

First and foremost, our literature review showed that studies on oral or buccal abuse of TOPs are rare. The practice remains in the grey area of substance abuse and illegality. Reports from national or regional poison center databases can indicate an order of magnitude of TOP abuse, although they are at risk for sampling error and 'unproven ingestion' bias.

Our review did find that oral and buccal abuse are the most frequently reported forms of TOP abuse. This particular route of administration is used for its psychoactive effects, in the context of suicide and for increasing analgesia. The pharmacology of TOPs shows that fast elevations in serum concentration can be expected, increasing the risk for respiratory depression and death. Because of the large quantity of fentanyl and the principle of buccal absorption, TOPs are an unpredictable drug of abuse in terms of dose-effect relationship.

The patient in our case showed several risk factors for opioid analgesic abuse, such as concomitant substance abuse and a history of depression. Even though he received chronic opioid therapy, the patient had never been referred to a pain specialist. Furthermore, the police did not conduct a full body-search when he was held in custody. When patients on transdermal opioid therapy are hospitalized in the context of drug intoxication, the body should be rigorously checked for remaining patches.

It is noteworthy that drug screening at the emergency department was negative for opioids. This is explained by the fact that routine drug tests do not generally screen for synthetic opioids. Therefore, in case of suspected opioid overdose, treatment with naloxone should never be postponed - regardless of the test results. When identification of the causative drug is imperative, specific drug analysis can be requested in consultation with the microbiologist.

As was illustrated in our case, a single bolus of naloxone is often insufficient in case of oral TOP intoxication (31). Instead, a continuous infusion of naloxone should be administered as proposed by Boyer (35). Concerning pain management, we decided to start paracetamol and tramadol ER. There have been some studies suggesting the use of tramadol ER for opioid withdrawal and in the context of chronic pain, with a recent study claiming lower propensities for abuse (38, 39). An alternative could be to start buprenorphine or methadone as maintenance therapy (37, 40).

No case reports were found concerning oral buprenorphine patch abuse. Claims have been made on the advantage of buprenorphine over fentanyl patches. These claims are based on partial agonistic effects of buprenorphine at the μ-receptor, leading to a ceiling effect for respiratory depression (41). Additionally, there are indications that buprenorphine has less euphoric effects than full opioid agonists in supratherapeutic doses (42). Poison center studies show that, even when adjusted for prescriptions dispensed, buprenorphine TOPs are less abused and less diverted than fentanyl TOPs (43, 44).

It is important to note that the majority of users obtain the patches via prescription. The claimed advantages of TOPs over other forms of opioid analgesics are the steady serum concentration and the convenience of use. It is important to weigh these modest therapeutic benefits against the risks of abuse. When confronted with patients at risk of abuse, physicians should actively inquire about oral or buccal abuse and discuss the associated health risks. Patients with chronic pain and comorbid opioid use disorder should be referred to substance abuse professionals or pain specialists.

Conclusion

Oral and buccal abuse of TOPs by ingesting or chewing opioid patches is the most common method of TOP abuse and frequently leads to hospitalization and death. Based on this review, we can label this

practice as an 'underrecognized, but potentially lethal' form of abuse. When chronic opioid therapy is initiated, patients should be regularly screened for opioid use disorder and referred to specialist care when necessary. However, it is pivotal that physicians perform a thorough risk-benefit evaluation before prescribing opioids for chronic pain.

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