RESEARCH ARTICLE

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SCIENCE

Allergic Contact Dermatitis to Fentanyl TTS with Good Tolerance to Systemic Fentanyl

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Abstract: Background: Fentanyl is primarily an opioid agonist. It is frequently used in general anesthesia as a potent analgesic. It can be administered either orally, transdermally or systemically. Adverse effects due to opium alkaloids are usually because of a non-specific histamine release. Only in a few cases, a true allergy mechanism could be involved. Immediate reactions to opioids are most frequent than delayed reactions. In the past years, delayed reactions have increased in frequency because of the wide use of Transdermal Therapeutic System (TTS) with several opioids for its potent analgesic properties.

Objective: The objective was to study delayed reaction to fentanyl TTS and cross-reactivity with other opioids.

Methods: A 52-year-old man with a diagnosis of pancreatic cancer who began treatment for a bone metastases pain with fentanyl TTS, at a dose of 50 micrograms per hour (mcg/h) is the subject of the study. After 10-15 days of treatment, he developed an itchy papulovesicular rash in the application site of the fentanyl TTS. Afterward, eczema and superficial desquamation just on the application site of the patch were observed. He changed several times the site of application, but always developing the same symptoms in every single application. Later on, he tolerated other opioids such as oral morphine or tramadol. An allergy workout was performed. We performed Patch Tests (PT) with fentanyl at a concentration of 10% in aqua (aq) and with buprenorphine 10% aq., in order to investigate probable cross-reactivity among other topical opioids.

Results: Readings were recorded at day 2 (D2) and day 4 (D4), with positive PT only with fentanyl at D2 (+++) and D4 (+++). We decided to perform a single-blind challenge test with buprenorphine 35 mcg/h in TTS, with a negative result. At this moment, fentanyl TTS was replaced by buprenorphine TTS, with good tolerance.

Conclusion: We present the case of Allergic Contact Dermatitis (ACD) due to hypersensitivity to fentanyl with good tolerance to buprenorphine. Positive PT in this patient suggests a type IV hypersensitivity mechanism. Allergic reactions to opioids are frequently immediate, but delayed reactions could appear, especially when the drug is administered topically.

Keywords: Allergic contact, buprenorphine, dermatitis, fentanyl, patch test, transdermal therapeutic system.

1. INTRODUCTION

Fentanyl is primarily an opioid agonist. It is frequently used in general anesthesia and as a potent analgesic with several ways of administration: Oral, transdermal and systemic. Immediate hypersensitivity reactions to opioids are most frequent than delayed reactions [1], but in the last

years, the use of Transdermal Therapeutic System [TTS] with several opioids has become usual, because of its potent analgesic properties, and may be delayed reactions to this group could be more frequently reported from now onward. Also, fentanyl cutaneous transdermal system may elicit anaphylactic reaction too, probably IgE mediated [2].

2. MATERIALS AND METHODS

A 52-year-old man with the diagnosis of pancreatic cancer was referred to our department for study. Due to the intense pain caused by generalized bone metastases, he was

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treated with fentanyl 50mcg/h TTS [Durogesic® [Janssen-Cilag, S.A. Lab], applying them on his back. Initially, the itchy papulovesicular rash was observed on the application site, several days after the beginning of the treatment. Afterward, he developed eczema and superficial desquamation limited to the application site of the TTS (Fig. 1). The patient was intensively affected with bone-ache, so he preferred the skin reaction with fentanyl TTS instead of managing pain without medication. Later on, he tolerated oral morphine or tramadol.

Fig. (1). Contact dermatitis with fentanyl TTS.

After obtaining informed consent from the patient, an allergy workout was performed: Patch Tests [PT] were applied on his forearm with fentanyl at a concentration of 10% in aqua [aq]. In order to know cross-reactivity among other topical opioids, we also tested PT with buprenorphine 10% aq [Nonwoven Patch Test Strips Curatest®; Lohman & Rauscher International, Rangsdorf, Germany].

3. RESULTS

Readings were recorded at day 2 [D2] and day 4 [D4] with positive PT only with fentanyl at D2 [+++] and D4 [+++] confirmed hypersensitivity to fentanyl.

Taking into account the underlying disease of the patient, and the need of giving alternative therapeutics to him, we performed a single-blind challenge test with subcutaneous fentanyl and buprenorphine 35mcg/h TTS, both with a negative result. Fentanyl TTS was replaced by buprenorphine TTS, with good tolerance.

4. DISCUSSION

We present a patient with the diagnosis of Allergic Contact Dermatitis [ACD] due to hypersensitivity to fentanyl, with good tolerance to fentanyl systemic administration and transdermal buprenorphine. A type IV hypersensitivity mechanism is suggested by positive PT.

In the last decades, TTS was widely used. It obtains a better distribution of the drug through the skin, with fewer side effects if the administration is systemic [3-5]. In this line, the increasingly widespread use of opioids in TTS in order to manage intense pain, has probably increased ACD to several opioids [5]. The fentanyl transdermal patch can

maintain constant fentanyl skin permeability for three days by maintaining a close contact with the skin.

Fentanyl and analogs thereof, such as alfentanil, carfentanil, lofentanil, remifentanil, sufentanil, trefentanil, are powerful synthetic opioids which have demonstrated utility in both human and veterinary medicine [6].

In human medicine, alfentanil, fentanyl, remifentanil and sufentanil have been granted regulatory approval for use as general anesthetics [7, 8]. Fentanyl containing lollipop for oral transmucosal administration and fentanyl containing transdermal patch have also been approved as analgesics for use in the treatment of chronic pain [8, 9].

The transdermal administration of these compounds for the treatment of both acute and chronic pain has been suggested and there are numerous patents describing various ways of transdermally administering fentanyl and analogs thereof [9-12]. These are believed to be representative and are incorporated herein by reference. These patents disclose that fentanyl can be administered from a topically applied ointment or cream or from a transdermal patch. A transdermal patch is typically a small adhesive bandage that contains the drug to be delivered and these bandages can take several forms. Fentanyl and analogs thereof are potent opioids having relatively narrow therapeutic indices. Because of the wide variations in individual pharmacokinetic (e.g., drug clearance rates) and pharmacodynamic response to opioids (e.g., the subjective nature of pain and the danger associated with overdose), patients typically need to be titrated upwards to determine the appropriate dose [12].

It has been discovered that by simultaneously administering particular combinations of drugs at particular dosage levels by means of a transdermal delivery system, the surgical stage of anesthesia may be induced in patients requiring such treatment. In addition, it has been found that profound sedation or an analgesic effect may be produced by means of a particular combination of pharmacological agents that are administered simultaneously by the transdermal administration [13].

Patches are commercially available for fentanyl, clonidine and scopolamine or they may be made using procedures that are described in the literature using routine experimentation to determine the optimum combination of materials and drug concentrations to achieve the desired therapeutic result [13, 14].

On the other hand, generalized systemic effects can occur if the medication is administered orally or intravenously, and this fact is unpredictable. In our patient, we assumed that some local factors could influence the development of the reaction, such as prolonged use and high local levels of fentanyl at the site of administration, thus, increasing the possibility of developing sensitization.

CONCLUSION

Allergy to opioids is infrequent but can occur any time, so we consider that it is important to perform a complete allergy workout in order to give alternative therapeutics to our patients.

The transdermal fentanyl administration has the advantage that the drug is not passed through liver first-pass metabolism, and has improved medication compliance, constant analgesic activity and lessened nursing effort. Fentanyl preparations administered transdermally may be used particularly in cancer patients. Several devices are approved for its therapeutic use [15].

CURRENT & FUTURE DEVELOPMENTS

In our opinion, the important point of discussion in these cases is to demonstrate tolerance to the systemic administration of the drug, if this is really essential. During the last year, TTS was added to the therapeutic options for patients with several comorbidities. We think that usually, they are well tolerated, but also, we think that allergic contact dermatitis to these devices could be more frequent in the future.

LIST OF ABBREVIATIONS

TTS = Transdermal Therapeutic System

ACD = Allergic Contact Dermatitis

PT = Patch Tests

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Informed written consent was obtained by the patient. The authors declare that they have followed the protocols of their work center on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in the study.

HUMAN AND ANIMAL RIGHTS

This case was regular clinical practice, and approved by the Ethics committee of our Hospital and confirmed by the patient. All clinical investigations were conducted according to the Declaration of Helsinki principles.

CONSENT FOR PUBLICATION

We accept the publication of this work by your Journal.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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CONFLICTS OF INTEREST

The authors declare they have no financial relationships with biotechnology and/or pharmaceutical companies interested in the subject matter or materials discussed in this manuscript.

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