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Drug Assessment Report
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Fentanyl pectin nasal

(▼PecFent®) spray in breaktrough pain. Nasal route of administration with no advantages regarding efficacy or safety

Abstract

- Fentanyl pectin nasal spray represents a different route of administration for opiods, although there is no improvement with regard to the safety profile.
- In comparison to oral morphine, pain relief after 15 minutes was favourable for fentanyl pectin nasal spray, while there were no differences between both treatments after 10 minutes.
- There is a risk of confusion regarding dose modifications with other formulations of fentanyl especially with Instanyl in cases of 100 µg doses: NEVER make a dose-for-dose switch (microgram for microgram).
- It can be an alternative in patients with oral intolerance.

Indications[1]

This drug is indicated for the management of breakthrough pain in adults that are already receiving opioid maintenance therapy for chronic cancer pain, defined as patients who take for a minimum period of one week:
· at least 60 mg oral morphine daily or
· at least 25 µg transdermal fentanyl every hour or
· at least 30 mg oxicodone daily or
· at least 8 mg hydromorphone daily or
· an equianalgesic dose of another opioid.

Mechanism of action and pharmacokinetics[1]

Potent opioid analgesic. Nasal absorption occurs rapidly. Metabolism occurs through CYP3A4 and elimination is mainly through urine. The spray produces droplets that form a gel in the nose, avoiding nasal drip, and swallowing of the drug.

Posology and form of administration[1]

The initial dose is 100 µg (one spray) even in patients treated with any other formulation of fentanyl. Adjustments should be made until an "effective" dose is reached, that in which adequate analgesia is reached without causing excessively intolerable adverse reactions during two consecutive episodes of breatkthrough pain. The efficacy of the drug should be evaluated during ensuing 30 minute interval after administration. If two applications are necessary (to administer 200 or 800 µg), then the same concentration of fentanyl pectin nasal spray (100 or 400 µg formulations) which should be applied in different nostrils.

No more than 4 applications should be given per day. Patients should wait at least 4 hours before treating another episode of breakthrough pain. Patients must be advised not to blow their noses after immediate administration of the drug. The patient is recommended to sit down during administration, mainly to avoid dizziness.

If treatment has to be discontinued, then a gradual downward titration of opioids should be carried out to avoid any effects of abstinence. If the drug is not used for five days, then re-prime by spraying once. The bottle should be discarded 60 days after opening.

The bottle of this fentanyl allows patients to confirm doses in tactile, audible and visual forms. It contains a mechanism that indicates when the 8 applications have been used and that the bottle should be discarded.

Clinical efficacy

Two double-blind, randomized trials have been published to evaluate the efficacy of nasal fentanyl, one versus nasal placebo[7,8] and another versus oral morphine.[11,12] There is also an open trial[13,14], that evaluated tolerance, acceptance and long-term safety. All of them carried out a previous titration period, and included only those patients who responded well initially and tolerated the drug.

'Oral morphine continues to be the elective choice in breaktrough pain'

Comparison to oral morphine

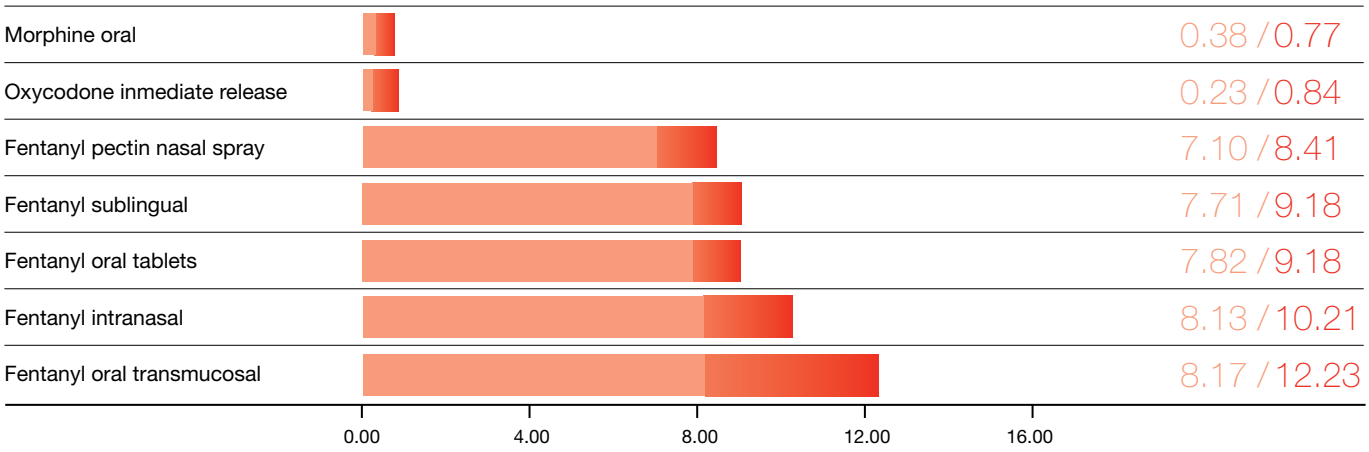
In this trial, 110 patients participated with a maximum duration of 21 days in the double-blind phase lasting 21 days. Treatment was given for up to 10 episodes of breakthrough pain. The dose of oral morphine for each patient was 1/6 of the total daily dose employed or that dose of morphine identified previously by the patient as the effective. The primary endpoint was the average difference in pain intensity after 15 minutes of administration. The result was 3.02 points for nasal fentanyl and 2.69 for morphine (total score, 11 points). The average difference (0.33 points) was statistically significant but of modest clinical relevance. The difference after 10 minutes (secondary endpoint) was not statistically significant.

On the whole, 97% of the episodes managed under nasal fentanyl and 96.2% of those under oral morphine did not need rescue medication. Dropouts reached 24%, 6% of the patients abandoned due to adverse effects, while 5% withdrew the drug due to lack of efficacy. Patients under fentanyl experienced more adverse reactions than those under morphine. The majority of the reactions were mild to moderate.

4	IMPORTANT THERAPEUTIC INNOVATION
3	MODEST THERAPEUTIC INNOVATION
2	SOME ADDED VALUE IN SPECIFIC SITUATIONS
1	**NO THERAPEUTIC INNOVATION**
0	INSUFFICIENT EVIDENCE

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.

COST RANGE OF DOSAGE UNIT IRRESPECTIVE OF THE DOSE (€)



Safety

Adverse reactions[1]

The adverse reactions are typical of opioid agents. The most severe are respiratory depression, circulatory depression, hypotension and shock. Nasal tolerance: There were no statistically significant differences between fentanyl and morphine.

Safety of the container

The container includes additional features that allows for verification of the dose in tactile, audible and visual formats. A lock-out mechanism indicates when 8 doses have been applied and the container should be discarded.

Contraindications[1]

Hypersensitivity to the active substance or any of the excipients.
Patients who have not received opioid therapy previously.
Severe respiratory depression or severe lung obstruction disorders.

Warnings and precautions[1]

There is a risk of clinically significant respiratory depression. Precaution is strongly advised in patients with COPD, elevated intracraneal pressure, cardiac disease, and in patients with nose-related disease. In case of nasal discomfort or epistaxis during administration another route should be considered. Tolerance and physical or psychological dependence can occur.

Use in special situations[1]

Pregnancy: do not use, unless clearly required. **Breastfeeding:** this drug is excreted in human breast milk and can cause sedation and respiratory depression in the infant. **Liver or kidney failure:** precaution is advised in cases of liver failure or moderate or severe renal failure. **Children:** it is not recommended in children under 18 years. **Elderly:** no information.

Interactions[1]

Avoid the concomitant use of nasal decongestants. This drug is not recommended with MAO inhibitors at least 14 days before initiating treatment. The concomitant use of partial opioid agonists/antagonists can antagonize the analgesic effect of fentanyl and produce abstinence symptoms in opioid dependent patients.
The concomitant use of other CNS depressants, including opioids, sedatives or hipnotics, general anaesthesia, phenothiazines, muscle relaxants, sedative antihistamine agents, and alcohol can potentiate this depressor effect. Interactions can also occur with inducers or inhibitors of CYP3A4.

EMA Risk Management Plan

The EMA has pointed out the need for educational material for physicians, pharmacists, and patients with information on the correct use and safety of the product.

Place in therapeutics

Fentanyl is a potent opioid used in clinical practice for many decades and whose efficacy and safety profile is well known. The use of the nasal route aims to achieve a quicker onset of action, a duration of the effect that covers the whole painful episode and in a non-invasive way.

It is better to avoid breakthrough pain than treat it. To do so, it is important to titrate adequately baseline analgesia, in order to reduce the frequency of incident pain, avoid pain at the end of dose, and facilitate the control of episodes of breakthrough pain.

In comparison to oral morphine, pain relief after 15 minutes of administration was more favourable for nasal fentanyl pectin, while there were no differences between both treatments after 10 minutes.

The profile of adverse reactions of both fentanyl and morphine is similar to other opioids, the most frequent effects include vomiting, somnolence, dehydration and nausea.

Nasal fentanyl is advantageous in patients where the oral route is not adequate, as in patients with nausea or vomiting, dry mouth syndrome, oral mucositis and gastrointestinal problems.

The variety of formulations available of fentanyl favours an individual-based approach to managing patients, but at the same time this can turn out to be its main disadvantage, as these formulations are NOT interchangeable among themselves and as a result this can lead to errors in dosage.

The AEMPS published an alert on possible prescription and dispensing problems with the other commercialized nasal fentanyl (Instanyl®) when both are applied at 100 µg/ application. On switching intranasal formulations, it is essential to make re-adjustments in the dose of the new drug, and NEVER make a dose-for-dose adjustment (microgram-for- microgram).

Presentations

PecFent® (Archimides Development UK) 100 and 400 µg 1 container 8 doses (67.31 €) and PecFent® 100 and 400 µg 4 containers 8 doses (227.13 €).

References and full report

Available at, www.dtb.navarra.es

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