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Drug Assessment Report
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Intranasal fentanyl

(▼Instanyl®) in breakthrough pain. A different route of administration with no advantages regarding efficacy or safety

Abstract

- Intranasal fentanyl represents an alternative route for the administration of opioids, although it does not improve the safety profile.
- It acts slightly earlier than transmucosal oral fentanyl but presents twice the amount of failures in breakthrough pain control.
- Possible risks of overdose have been highlighted as well as the potential danger for children and the family, given the nasal spray device.
- There is a risk of confusion regarding doses with other presentations of fentanyl, especially with PecFent® when administering doses of 100 µg: NEVER carry out a dose-for-dose change in medication (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 equianalagesic dose of another opioid.

Mechanism of action and pharmacokinetics[1]

Potent opioid analgesic. Nasal absorption and distribution occur rapidly. The elimination half life is 3-4 hours. Metabolism occurs through CYP3A4 and elimination is mainly through urine. The tmax is reached after 12-15 minutes.

Posology and form of administration[1]

The initial dose is 50 µg and is applied in the nasal fosa. This dose can be repeated after 10 minutes. Doses should be increased when the patient requires more than one dose for an episode of breakthrough pain during several consecutive episodes of pain. If the patient demands continuously for at least 4 consecutive episodes of breakthrough pain per day, it may be necessary to adjust the patient's maintenance opioid therapy. If the patient presents intolerance or persistent adverse reactions, then the dose should be reduced or the nasal fentanyl replaced by other analgesics.

There is concern about the potencial danger of the device with regard to overdose, especially in children. As a result the manufacturer has been petitioned to carry our relevant modifications.

Clinical efficacy

Two phase III studies have been carried out, one versus placebo[2] and the other versus transmucosal oral fentanyl (Actiq®).[4] Before evaluating efficacy both trials underwent a titration phase, so that only those patients who responded well initially and tolerated the drug were included.

Comparison to transmucosal oral fentanyl

This open, cross-over, randomized trial compared the efficacy and tolerability of nasal fentanyl to transmucosal oral fentanyl. The primary endpoint was time to "significant" pain relief.

The average time in the case of nasal fentanyl was 10.6 minutes, while in the case of transmucosal oral fentanyl it was 15.7 minutes. The differences were statistically significant although clinical relevance was only discrete. A second dose of nasal fentanyl could be repeated after 10 minutes and after 30 minutes in the case of transmucosal oral fentanyl.

In 58% of the patients treated with nasal fentanyl and in 30% of those under transmucosal oral fentanyl a second dose was required. Rescue medication was needed in 7.8% of the patients under nasal fentanyl and 4.9% in those under transmucosal oral fentanyl.

The incidence of withdrawals was similar in both groups, 8.2% in the case of nasal fentanyl and 6.8% in the case of transmucosal oral fentanyl.

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

Safety

Adverse reactions[1]

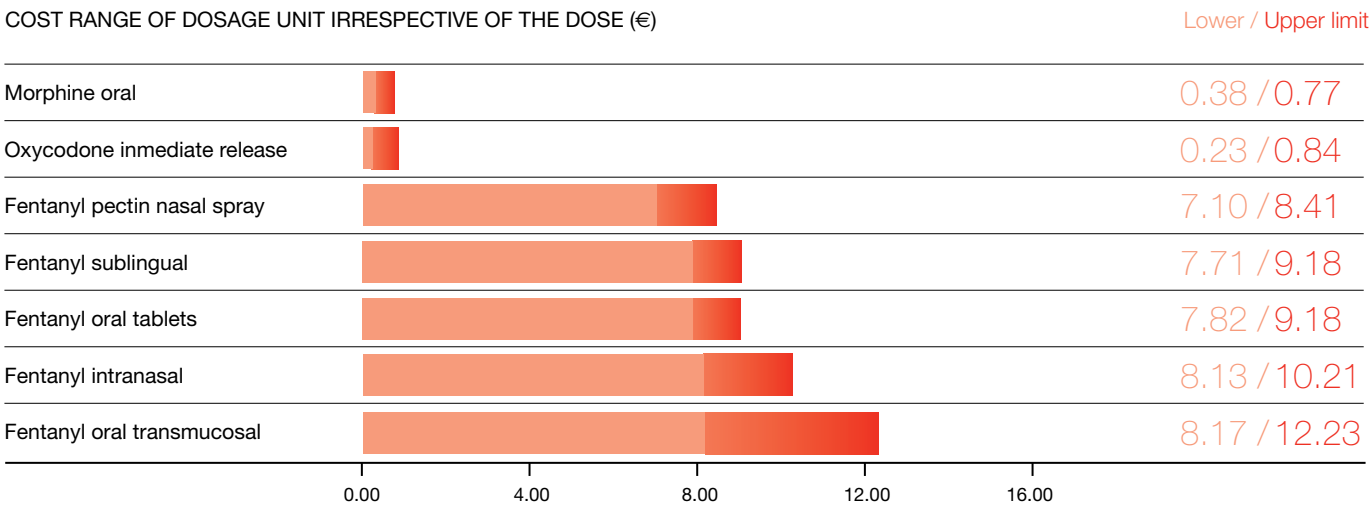
Typical adverse reactions of opioids can occur, the most severe, respiratory depression, circulatory depression, hypotension and shock.

Contraindications[1]

Hypersensitivity to the active substance or any of the excipients.
Use in patients who have not received previous treatment with opioids.
Severe respiratory depression or severe obstructive lung disorders.

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.



Warnings and precautions[1]

There is a clinically significant risk of respiratory depression. Precaution is strongly advised in cases of COPD, elevated intracraneal pressure, cardiac disease, and in patients with nasal related diseases. If considerable discomfort affects the nose or epistaxis during administration, then an alternative route should be considered. Tolerance and physical or psychological dependence can occur.

Use in special situations

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 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 to modify the package to avoid possible risks of overdose, the potential danger of use by children and within the family environment, and the development of educational materials informing on the correct and safer use of this product.

Place in therapeutics

Fentanyl is a very potent opioid which has been employed in clinical practice for decades and whose efficacy and adverse effects profiles are well known. The nasal administration attempts to attain rapid initial action, duration of the effect throughout the pain episode and through a non-invasive formulation.

It is better to prevent the onset of breakthrough pain than treat it. To do so, it is fundamental to titrate basal analgesia adequately, which reduces the frequency of incidental pain, avoids pain at the end of dose and facilitates the control of episodes of breakthrough pain.

In the only study including a comparative active substance, the onset of action of nasal fentanyl was slightly ahead of transmucosal oral fentanyl, but the former presented twice the amount of failures in controlling episodes of breakthrough pain.

Nasal fentanyl can be an alternative in patients where the oral route is not adequate, for example, 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 management, but simultaneously creates a problem because the formulations are not themselves interchangeable and therefore can lead to errors in dosage.

The AEMPS published an alert regarding problems on prescription and dispensing with the other marketed nasal fentanyl (PecFent®) when both are administered at the dose of 100 µg/spray. Switching between one intranasal formulation to another require new dose adjustments of the new drug and dose-for-dose adjustments (microgram-for-microgram) should NEVER be done.

Presentations

Instanyl® (Nycomed, Takeda) 50, 100 and 200 µg 6 single doses (61.26 €), Instanyl 50, 100 and 200 µg 10 doses (102.09 €) and Instanyl 50, 100 and 200 µg 40 doses (325.01 €).

References and full report

Available at, www.dtb.navarra.es

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