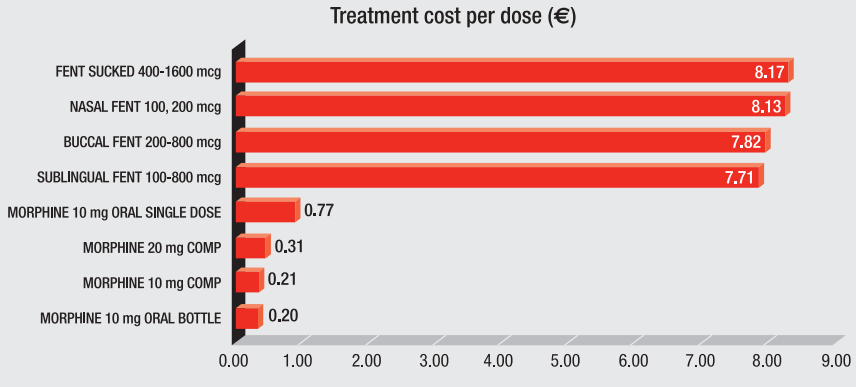
www.dtb.navarra.es

12/2011

Sublingual fentanyl citrate ▲(Abstral®) For breakthrough pain in cancer patients

Another formulation in a perilous and lucrative oral fentanyl market



Therapeutic indications[1]

Management of breakthrough pain in adult patients using opioid therapy for chronic cancer pain. Breakthrough pain is a transient exacerbation of otherwise controlled chronic background pain.

It is considered that a patient is under opioid maintenance therapy for chronic cancer pain when receiving at least oral morphine 60 mg/d, transdermal phentanyl 25 g/h, oxicodone 30 mg/d, hydromorphone 8 mg/d, or equivalent doses of another opioid drug during one week or longer.

Mechanism of action and pharmacokinetics[1]

Potent opioid analgesic rapidly absorbed by the oral mucosae (30 minutes after administration) and much slower in the gastrointestinal tract where a first pass effect occurs. The bioavailability is estimated to be 70% and the elimination half life is 7 hours. It is metabolized in the liver and 75% of the dose is excreted in urine.

Posology and methods of administration[1]

It is administered directly under the tongue in the deeper pocket until it dissolves complete-

Exclusive in breakthrough pain in cancer patients

*

- Sublingual fentanyl is indicated solely for breakthrough pain in cancer patients, whenever pain is characterized by persistence in time, and patients are already under management with chronic opioid agents.
- The evidence of sublingual fentanyl efficacy is scarce, with only one study available comparing it to placebo. There are no comparative studies with different formulations of fentanyl available on the market, or any of the other immediate release opioids.
- This potent opioid is not safer than other opioids and bears a similar adverse reaction profile to the other opioids.
- It requires an adjustment and titration phase to establish the effective dose for each patient. Interchanges of the different formulations of oral fentanyl at the same doses is not possible as they are not equivalent.

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.

ly. It should not be swallowed, chewed or masticated. Patients should be cautioned not to eat, or drink anything until the tablet is completely dissolved. In patients with dry mouths, water can be used to humidify the oral mucosae before taking the tablet.

Before adjusting doses of sublingual fentanyl, it should be confirmed that baseline pain is under control with the chronic treatment of opioids and that no more than four daily episodes of irruptive pain occur.

The initial dose is 100 µg and the optimal dose is determined individually by increased dose adjustments. Before administering complementary sublingual fentanyl, patients should wait 15-30 minutes when adequate relief has not been reached. The dose of the complementary sublingual tablet in case of inadequate analgesia could be either 100 or 200 µg according to drug information[1]. Once the adequate dose is determined then it should be maintained and consumption limited to four times a day (8 tablets). The tablets should be taken only in cases of breakthrough pain.

No changes to sublingual fentanyl tablets should be made from other formulations at equal doses. This is due to the different absorption profiles, which makes it unviable to change from one oral formulation to another at the same dose. New dose adjustments are required.

Clinical efficacy

There are no comparative studies with other treatments employed in the management of breakthrough pain like immediate release oral morphine or the different formulations of fast acting fentanyl.

The efficacy of sublingual fentanyl has been studied in one controlled trial, carried out on 131 adult cancer patients that suffered 1 to 4 episodes of breakthrough pain, treated with a fixed daily oral regimen of 60-1000 mg or 50-300 µg per hour transdermal fentanyl. In a previous stage the single effective dose of sublingual fentanyl (100, 200, 300, 400, 600 or 800 µg) is determined to treat am episode of breakthrough pain. In the double blinded phase patients (n=66), received 7 doses of sublingual fentanyl and 3 received placebo randomly for 2 weeks. In the open phase the safety profile was evaluated in 72 patients for 12 weeks, but only 25 patients completed the study.

The primary endpoint defined as the sum of the difference in pain intensity (SPID) after 30 minutes of administration was significantly greater with sublingual fentanyl compared to placebo (49.5 versus 36.6 p = 0.0004). This significant improvement was maintained 60 minutes after the initial dose (143.0 versus 104.5, p = 0.0002).

The proportion of responders with sublingual fentanyl was 86.9% and 64.9% with placebo.

Safety

Adverse reactions[1]

Similar to opioids. The most frequent adverse reactions (≥1/10) are: dizziness, headache, somnolence, nausea, fatigue, and the frequent (≥1/100, <1/10): vasovagal reaction, hypoesthesia, paresthesia, hyperacusia, vision abnormalities, respiratory depression, rhinitis, pharyngitis, vomiting, abdominal pain, diarrhoea, constipation, dyspepsia, dry mouth, skin eruptions, pruritus, orthostatic hypotension, blushing, flushing, asthenia, local irritation, depression, anorexia, difficulty in concentration and euphoria.

Contraindications[1]

Hypersensitivity to the main active substance or excipients. **Patients who have not previously received treatment with opioids.** Severe respiratory depression or severe COPD.

Warnings and precautions[1]

Patients should be warned not to drive or use machinery if they feel dizzy, drowsy or suffer from blurred or double vision while taking the fentanyl tablets. Special attention with regard to dose adjustments should be given to patients with non severe COPD or other disorders that may predispose them to respiratory depression. Precaution should be taken in patients with bradiarrhythms, and with hypovolaemia and hypotension and those with mouth ulcers or mucositis.

Repeated administration of opioids such as fentanyl can induce tolerance and physical and/or psychological dependence.

Use in special situations[1]

Pregnancy, lactation and children: do not use. **Liver and renal impairment and elderly:** precaution when adjusting doses to detect signs of fentanyl toxicity that would require a reduction in dose.

Interactions[1]

Potent inhibitors of the CYP3A4 such as ritonavir, ketoconazole, itraconazole and erythromycin or moderate inhibitors such as erythromycin, fluconazole, and verapamil can increase the opioid effects.

The administration with other depressors of the CNS can cause respiratory depression, hypotension and profound sedation. Sublingual fentanyl is not recommended in patients under MAO inhibitors (tranilcipromine, moclobemide, selegiline) two weeks before as an unpredictable and severe increase in MAO inhibitor potential has been published.

It is not recommended to simultaneously offer buprenorphine, nalbufin, pentazocine as they may produce abstinence syndrome in patients with opioid dependence.

Place in therapeutics

In patients with cancer, the incidence of temporary exacerbations of pain, known as breakthrough pain is common. Breakthrough pain is characterized by a quick onset, great intensity (≥7 on a scale of 0-10) and a short duration (average 30 minutes)[5]. Avoiding its incidence is better than treating it and so, it is fundamental to carry out adequate titration of the baseline analgesia.

The recommended drugs for breakthrough pain are immediate release morphine and fentanyl[6]. Sublingual fentanyl is only indicated in breakthrough pain affecting cancer patients, whenever the underlying pain is persistent and is managed by chronic use of opioids. It has no indication in non-cancer related pain.

Currently, there are no studies directly comparing the different formulations of oral fentanyl available (tablets to suck, buccal tablets) or with immediate release morphine. The efficacy of sublingual fentanyl has only been shown to be greater than placebo in one published study. The onset of action and magnitude of effect (rescue medication, responsive patients (≥30% after 30 minutes) is similar to other formulations of oral fentanyl.

Some of the inconveniences of these formulations include the difficulty to adjust doses and its high cost. The variety of fentanyl formulations available favours individual therapy, but at the same time makes it its main disadvantage: a wide range of existing formulations, with no form of exchanging them can lead to errors in dosage.

Presentations

Abstral® (ProStrakan) 100, 200, 300, 400 µg 10 y 30 sublingual tablets (91.79 y 231.2 €); 600, 800 µg 30 sublingual tablets (231.2 €).

References

A complete report on sublingual fentanyl citrate is available at: http://www.dtb.navarra.es

Servicio Navarro de Salud
Osasunbidea

INFORMATION:
Servicio de Prestaciones Farmacéuticas Plaza de la Paz s/n, 4ª planta - 31002 Pamplona **T** 848429047 **F** 848429010