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Editorial comment

# Transmucosal fentanyl for severe cancer pain: Nasal mucosa superior to oral mucosa?

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In this issue of the *Scandinavian Journal of Pain* I. Prieto and co-workers from Spain describe an observational study of fentanyl in a pectin solution for intranasal transmucosal administration for severe incident breakthrough pain from positioning the patient for focused radiation therapy for advanced cancer conditions [1].

## 1. Fentanyl is a good candidate for transdermal and transmucosal administration

### 1.1. Transdermal application of a fentanyl patch

Fentanyl is a lipophilic opioid that is absorbed when administered in a patch on the skin, and because fentanyl is such a potent opioid, the amounts absorbed are enough to relieve chronic cancer and chronic non-cancer pain. The hydrophilic morphine does not penetrate the skin in sufficient amounts for the less potent morphine to cause pain relief. Transdermal application of fentanyl is also too slow for relief of acute pain after surgery or for severe breakthrough pain episodes in patients on long-term opioid treatment for chronic pain. Attempts to increase the speed of transdermal absorption by applying electrical forces were promising, but the mechanics turned out to be unreliable and unsafe.

### 1.2. Transmucosal application of fentanyl

Administered on the oral or nasal mucosa fentanyl is absorbed rapidly enough and in amounts sufficient to relieve even very severe acute pain and break-through pain. Ever since the "fentanyl lollypop" (Actiq®) was introduced some years ago, new and improved versions of fentanyl for transmucosal administrations have been marketed.

*Effentora® sublingual tablets* dissolve slowly and therefore have a relatively long onset of action.

*Abstral® sublingual tablets* dissolve very rapidly [2] and are not dependent on saliva because it is enough to rinse a dry mouth with water before placing the tablet under the tongue. Lack of saliva, a common problem in advance cancer patients with dry mouth from dehydration and from drugs that have anticholinergic effects, is not necessarily a problem when using Abstal®: With little or no saliva in the mouth the patient is not able to swallow the dissolved tablet before it is absorbed. Swallowing a tablet that takes a longer time to dissolve, reduces the effect because fentanyl is absorbed from the stomach but is almost completely removed from the blood during the first pass through the liver. Therefore, very little reaches the brain and the opioid receptors there. If there is a lot of saliva, swallowing is more difficult to avoid.

*Instanyl® nasal spray* is well documented to cause rapid transmucosal absorption and rapid onset of pain relieving effect [3,4]. In the Instanyl® nasal spray the fentanyl is dissolved in a watery solution. Depending on the body position of the patient, some of the watery fentanyl-containing solution may drip from the nose or flow back to the nasopharynx and will be swallowed, loosing some of its effect. In most patients needing transmucosal administration of fentanyl for severe pain, this is not a practical problem [3,4].

*PecFent® nasal spray* contains fentanyl dissolved in a solution that becomes a slightly sticky gel in contact with the nasal mucosa [5]. This prevents dripping out of the nose or back into the nasopharynx. This may be an advantage of PecFent® when the patient is restlessly moving in a crisis situation with excruciating breakthrough pain. Once the pectin solution is placed in the nasal cavity, it stays on the mucosa better than the alternatives.

This was the reason Prieto and co-workers chose to study PecFent® for treating severe breakthrough pain precipitated by positioning their patients for radiotherapy. Most of the patients had enough pain relief quickly enough so that the radiotherapy treatment could be performed [1]. The alternative could be deep sedation or full general anaesthesia with an intubated patient. This would require a full anaesthesia team, would delay the treatment procedure and cost more resources [1].

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## 2. Conclusions and implications

We now have several marketed transmucosal fentanyl drugs all intended for rapid relief of severely intense breakthrough pain in cancer patients already treated with opioid analgesics for pain related to their malignant disease. It is important that the patients are able to administer the breakthrough pain medication themselves. The patients will prefer the alternatives with the most rapid onset and most stable effect from a given dose. It is also important that it is practical and easy for the patient to administer the drug and to keep track of the doses taken. It is extremely important that the drug is not easily available for relatives, children and grandchildren in particular. A tablet or one nasal spray can be rapidly fatal in the hands of children, or other persons who are naïve to opioids.

These drugs are increasingly used for cancer patients with pain that fluctuates in intensity: when the patient is able to self-administer a transmucosal, quickly dissolving sublingual tablet or a nasal spray when they need quick and potent pain relief, the daily total dose may be less than when they are given fentanyl transdermally around the clock. All adverse effects from opioids are dose-related. For the patient to be able to control their opioid medication with transmucosal fentanyl may increase quality of pain relief [6]. They will feel more in control of their pain and may obtain better health related quality of life.

## Conflict of interest

None declared.

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