Efficacy of intranasal fentanyl spray versus other opioids for breakthrough pain in cancer

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CRD summary
This review compared the effectiveness of intranasal fentanyl spray, oral transmucosal fentanyl citrate, fentanyl buccal tablet, and oral morphine break-through cancer pain treatment; it concluded that intranasal fentanyl spray provided the greatest improvement (greatest reduction in pain within 15 minutes of administration). Overall, the results were clearly reported and appeared reliable, and the authors’ conclusions reflect the results.

Authors’ objectives
To compare the effectiveness of intranasal fentanyl spray, oral transmucosal fentanyl citrate, fentanyl buccal tablet, and oral morphine for the treatment of break-through cancer pain.

Searching
MEDLINE, EMBASE and BIOSIS Previews databases were searched for relevant studies from 1996 to October 2007. Search terms were reported. Conference proceedings were also searched. Pre-published data from the clinical development programme for intranasal fentanyl spray were also included.

Study selection
Eligible studies were randomised controlled trials (RCTs) that looked at the management of break-through cancer pain and allowed comparison between oral morphine, intranasal fentanyl spray, fentanyl buccal tablet and oral transmucosal fentanyl citrate. Eligible participants were defined as adult cancer patients suffering from break-through pain and treated with opioid analgesics for the management of background pain. Eligible trials had to report pain intensity difference as an outcome (defined as the difference between the pain intensity at specified time points following the start of the episode) and the pain intensity at the start of the episode.

In the included trials, mean initial pain intensities ranged from 5.9 to 6.9 (on an 11 point scale that ranged from 0 to 10). The mean age of included patients ranged from 54 to 62 years; the most common tumour types were lung, breast and colorectal tumours. The minimum episode frequency for inclusion in intranasal fentanyl spray trials was three per week, and once a week for other trials; the maximum episode frequency was four episodes per day. The included trials were conducted in the USA or Europe.

It was unclear how many reviewers performed the study selection.

Assessment of study quality
The reviewers did not state that they performed a quality assessment, although some trial design details relating to quality were reported (such as the use of randomisation and blinding).

Data extraction
Data were extracted to calculate initial (t=0) pain intensities and pain intensity differences, with 95% credible intervals (95% CrI), at time intervals of 15 minutes, 30 minutes, 45 minutes, and 60 minutes following the start of the break-through cancer pain episode.

The authors did not state how many reviewers performed the data extraction, although data were checked by a second reviewer.

Methods of synthesis
The reviewers pooled data using a fixed-effect Bayesian mixed-treatment comparison model. For missing data, average pain intensity differences were calculated using adjacent time points.

A sensitivity analysis to assess the impact of a single trial on pooled results was performed, but it was unclear whether
this was planned a priori.

**Results of the review**

Six double-blind RCTs were included in the review (n=594 patients, range 86 to 139).

Using the mixed-treatment comparison model, intranasal fentanyl spray (1.9 points, 95% CrI 1.5 to 2.4), fentanyl buccal tablets (1.7 points, 95% CrI 1.3 to 2.0), oral transmucosal fentanyl citrate (1.5 points, 95% CrI 1.0 to 2.1) and oral morphine (1.0 point, 95% CrI 0.2 to 1.8) all had better outcomes (reduction in pain on 11-point scale) than placebo 60 minutes after administration (pain intensity difference at 60 minutes).

Based on indirect comparison, intranasal fentanyl spray appeared to reach a higher level of effectiveness (greater pain reduction) earlier than fentanyl buccal tablets, oral transmucosal fentanyl citrate or oral morphine; it was statistically significantly more effective than the other treatments 15, 30 and 45 minutes after administration.

**Authors' conclusions**

Based on the available evidence, intranasal fentanyl spray was likely to provide the greatest improvement in the treatment of breakthrough cancer pain; due to the slow onset of effect, oral morphine could not be considered an appropriate treatment for breakthrough cancer pain.

**CRD commentary**

This review addressed a clear research question using appropriate study selection criteria. Relevant databases were searched, with no date or language restrictions and with efforts to identify unpublished studies, reducing the risk of bias at this stage. It was not clear how many reviewers were involved in the study selection and data extraction stages of the review process (although data extraction was checked by a second reviewer), so it was not possible to exclude the possibility of reviewer error and bias in these review processes.

No trial quality assessment was reported, so it was not possible to rule out the risk of methodological issues within included trials biasing the reported results; however, only RCTs were eligible for inclusion, which reduced the possible extent of this bias. Sufficient primary trial details were reported. The method of synthesis appeared appropriate. As it was a relatively novel method of synthesis, further explanation of the method and assumptions required may have been a benefit, along with appropriate sensitivity analyses to investigate the effects of trial quality and clinical heterogeneity in reported outcomes.

Overall the results were clearly reported and appeared reliable, and the authors' conclusions reflect the results.

All of the reviewers disclosed financial links with Nycomed (manufacturers of intranasal fentanyl spray evaluated and funders of the review); one reviewer was an employee.

**Implications of the review for practice and research**

**Practice:** The authors stated that, where breakthrough cancer pain peaks within minutes, intranasal fentanyl spray should be administered as the optimal treatment.

**Research:** The authors did not state any implications for research.

**Funding**

Nycomed (manufacturers of Instanyl or intranasal fentanyl spray evaluated in the review).

**Bibliographic details**


**PubMedID**
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.