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The objective of this study was to demonstrate the efficacy, safety and patient acceptability of the use of intranasal sufentanil for cancer-associated breakthrough pain. This was a prospective, open label, observational study of patients in three inpatient palliative care units in Australia. Patients on opioids with cancer-associated breakthrough pain and clinical evidence of opioid responsiveness to their breakthrough pain were given intranasal (IN) Sufentanil via a GO Medical™ patient controlled IN analgesia device. The main outcome measures were pain scores, need to revert to previous breakthrough opioid after 30 min, number of patients who chose to continue using IN sufentanil, and adverse effects. There were 64 episodes of use of IN sufentanil for breakthrough pain in 30 patients. There was a significant reduction in pain scores at 15 ($P < 0.0001$) and 30 min ($P < 0.0001$). In only 4/64 (6%) episodes of breakthrough pain did the participants choose to revert to their prestudy breakthrough medication. Twenty-three patients (77%) rated IN sufentanil as better than their prestudy breakthrough medication. The incidence of adverse effects was low and most were mild. Our study showed that IN sufentanil can provide relatively rapid onset, intense but relatively short lasting analgesia and in the palliative care setting it is an effective, practical, and safe option for breakthrough pain. *Palliative Medicine* (2009); **23**: 54–58

Key words: breakthrough pain; cancer; opioid; sufentanil

Introduction

Most patients with cancer-associated pain can achieve acceptable baseline pain control with treatment based on pain mechanisms and the World Health Organisation (WHO) analgesic ladder approach. However, up to 60% of patients suffer from episodes of breakthrough pain, in which there are transitory flare-ups against a background of otherwise well controlled pain.[1] Portenoy and Hagens' three month audit of inpatients in a cancer centre showed that of 70 patients with moderate pain or less and on a stable dose of opioids, 63 (90%) had at least one episode of breakthrough pain per day and that 41% of these episodes were of rapid onset, that is, within 3 min and of relatively short duration, median 30 min. In patients with multiple bone metastases, these episodes often occur with movement such as showering or walking. The standard palliative care management of breakthrough pain is to give an immediate release opioid medication, either as an oral or subcutaneous bolus as needed.[2] This is known as "breakthrough" or "rescue" dosing. Given the features of breakthrough pain, the ideal characteristics of a breakthrough medication are rapid onset, early peak effect, and duration of action of no more than 1–2 hrs.[1] When opioids such as morphine or oxycodone are used as breakthrough medication, either orally or subcutaneously, the effect is neither quick nor short acting. Onset is delayed for at least 30 min and the effect lasts for 2–3 hrs. Intermittent intravenous (IV) bolus dosing or patient controlled IV analgesia (as is used short-term post-operatively) is rarely feasible in an inpatient palliative care unit, and even less so in a home environment, due to the need for continuous IV access, relatively expensive and bulky devices and the risks associated in patients with poor cognition.

Compared to morphine, oxycodone and hydromorphone, the fentanyl series of drugs have higher lipid solubility (hence rapid and effective transmucosal absorption plus enhanced blood brain penetration), higher potency (hence potentially fewer adverse effects), a better therapeutic index (hence greater safety at high doses) and a shorter duration of action.[3] These characteristics make

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them particularly suitable for transmucosal delivery. Sublingual, buccal and intranasal (IN) dosing all bypass first pass hepatic metabolism, and allow for rapid absorption by an area with a rich blood supply.

Helmers, *et al*.[4] compared IV and IN sufentanil as premedication prior to elective surgery. The IV route resulted in a faster onset (10 compared to 20 min); however, mean concentrations at 30 and 60 minutes were similar. The incidence of respiratory depression was higher in the IV group. Bioavailability after IN administration was 78%. A small number of studies on IN fentanyl as an analgesic in palliative care have been reported.[5,6] Minimal adverse effects were reported but due to the fact that the doses delivered were low (20 mcg) and multiple doses were needed before meaningful pain relief was achieved. The dose of 20 mcg fentanyl per administration was dictated by the need to keep the volume administered low as otherwise it will be swallowed rather than absorbed transmucosally.

In view of these promising preliminary data from other centres,[7] it was decided to evaluate the administration of the fentanyl analogue sufentanil by the IN route. Fentanyl and sufentanil are both only commercially available as 50 mcg/ml solutions. However, due to its 10 times greater potency, low volumes of sufentanil provide clinically meaningful doses in the opioid tolerant palliative care population.

A pilot study looking at seven applications in four patients suggested IN sufentanil was safe, efficacious and user friendly and that 9 mcg IN sufentanil was a safe initial dose.[8] The objective of the study reported here was to demonstrate the efficacy, safety and patient acceptability of the use of IN sufentanil for cancer-associated breakthrough pain in a larger number of patients, based on the dosage and safety data gained from the pilot study.

Methodology

The study was conducted in two phases. An initial dose titration phase similar to the pilot trial was followed by an ongoing treatment phase once an effective and safe dose was determined for each patient. All patients were inpatients at one of three palliative care units in Australia.

Inclusion criteria were patients who had cancer-associated pain, were non-opioid naïve (on opioids for at least one week) and who had clinical evidence of opioid responsiveness. The patients also had to have had controlled background pain and stable doses of long acting opioids. Exclusion criteria were terminal phase of illness, cognitive impairment severe enough to hinder reliable verbal rating scale (VRS) reporting, an inadequate command of English to allow reliable VRS reporting, respiratory failure, a known history of substance abuse or nasal deformity/bleeding/infection such as to contra-indicate nasal drug administration.

The sufentanil was delivered by a GO Medical™ patient controlled IN analgesia (PCINA) device.[9] This is a 5 or 10 ml bottle that delivers 0.18 ml as a fine spray with each depression of the nasal applicator. Using a 50 mcg/ml concentration of sufentanil means that there is 9 mcg of the drug delivered per spray/depression. The study was approved by the human research ethics committee at each participating institution.

Dose titration phase

Patients were shown how to use the PCINA, and then when they experienced an episode of breakthrough pain, under nursing or medical staff supervision, they used one spray of IN sufentanil into one nostril. If more than one dose was needed, then they were given into the alternate nostril.

And then the dose escalation is as follows:

Step I: A 9 mcg dose, which was repeated at 10 and 20 min if required and drowsiness scale evaluation was less than 2. If ineffective at 30 min, usual opioid breakthrough was given and Step II was followed for next episode.

Step II: 18 mcg dose, which may be repeated at 10 and 20 min if required and drowsiness scale evaluation was less than 2. If ineffective at 30 min, give usual opioid breakthrough and go to Step III for next episode. As for above

Step III: 36 mcg dose, which may be repeated at 10 and 20 min if required and drowsiness scale evaluation was less than 2. If ineffective at 30 min give usual opioid breakthrough and conclude study. As for above

Data was entered directly onto dedicated forms at 0, 5, 10, 15, 30, 60 and 120 min. Data collected included pain on a 0–10 VRS: 0 = no pain, 10 = worst possible pain, drowsiness on 0–4 scale: none (0, patient alert); mild (1, occasionally drowsy, easy to rouse); moderate (2, frequently drowsy, easy to rouse); severe (3, somnolent, difficult to rouse); unconscious (4, unrousable), respiratory rate (RR), oxygen saturations, presence or absence of nausea, vomiting or confusion, nasal pain or bleeding. Additionally, patients were asked after each episode of IN sufentanil whether this had provided worse, the same or better relief than their usual opioid breakthrough agent.

Ongoing phase

During the ongoing phase the titrated effective dose was used for all subsequent episodes of breakthrough pain. If IN sufentanil was effective, any patient later in the trial, who was discharged, was given the option of use at home

with follow-up monitoring by a community palliative care service.

The outcomes measured were pain on a 0–10 VRS, the need to revert to the previous breakthrough after 30 min and the number of patients who chose to continue in the ongoing phase. The adverse effects recorded included drowsiness score 2 or greater, RR less than 10, a significant decrease on oxygen saturation (SPO_2 less than 90), nausea/vomiting, confusion, and nasal bleeding or pain.

The Friedman test was used to assess the statistical significance of change in VRS at 15 and 30 min.

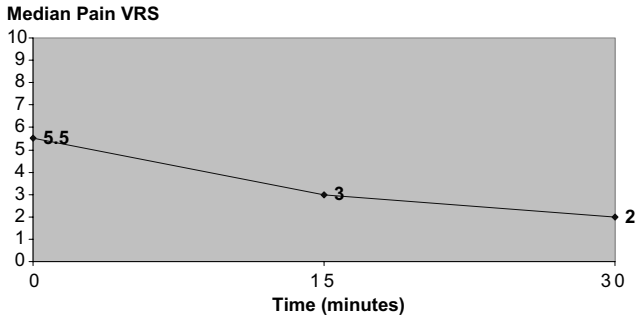

Figure 1 Median pain VRS over time.

Results

Data was available for 30 patients who had 64 episodes (in total for both phases) of IN sufentanil. The range of primary malignancies was in line with those commonly represented in an inpatient palliative care unit with the most common cancers being colorectal, lung and breast. The most common types of pain mechanism for the breakthrough pain were neuropathic (11 patients), visceral (7 patients), somatic (6 patients), but also included mixed somatic/neuropathic (5 patients), and unknown mechanism in one patient. A variety of opioids were used for background and breakthrough analgesia (see Table 1) but morphine was the commonest in 43 and 60% of patients respectively.

The median VRS scores (mean, SD) were 5.5 (5.9 ± 1.8), 3 (3.3 ± 2.3), 2 (2.5 ± 2.4) at 0, 15 and 30 min respectively (Figure 1). There was a significant reduction in pain scores at 15 ($P < 0.0001$) and 30 minutes ($P < 0.0001$). If response to an analgesic is taken as a percentage pain intensity difference (PID%) ≥33%,[10] then (at 30 min) 40 out of the 64 episodes (63%) could be counted as responding to the medication. The dose range for these responsive episodes was from 9 to 108 mcg, with 18 mcg being the median dose. The majority (63%) of these responsive episodes were well controlled by IN sufentanil 18 mcg (i.e. two sprays) or less.

Twenty-three of the patients rated the IN medication as better than their normal breakthrough medication. That only six patients continued the medication on discharge or at the end of the trial was due to decline in health status or patient death because of progression of the underlying cancer. Only in 4/64 episodes (6%) of use did the patient have to revert to their usual breakthrough after 30 min.

There was no correlation with patients' 24 hr opioid dose or a patient's usual opioid breakthrough, and the effective IN sufentanil dose. For example, there were two different patients, one on a usual breakthrough of morphine 40 mg s/c, the other on morphine 2.5 mg s/c, both achieved good pain relief at 15 min, after IN sufentanil 18 mcg with no adverse effects in either.

Table 1 Opioid usage prior to IN sufentanil

Opioid	Background opioids usage – no. (%)	Breakthrough opioids use – no. (%)
Morphine	13 (43)	18 (60)
Fentanyl	6 (20)	1 (3)
Oxycodone	6 (20)	7 (23)
Sufentanil	3 (10)	–
Methadone/Morphine	1 (3)	–
Hydromorphone	1 (3)	4 (13)

Adverse events

Drowsiness with a score of 2 or greater occurred with three episodes of IN sufentanil. Nausea occurred in two uses of the medication, and headache in one. In one of the episodes of nausea this was associated with facial flushing and sweating. One trial was abandoned when a patient's RR fell from 20 to 16, although the oxygen saturations were normal. This patient also experienced moderate drowsiness and the VRS decreased from 9 initially to 2 at 30 min.

Five patients withdrew from the trial – one due to headache associated with IN sufentanil; one due to severe osteoarthritis in both hands making it too difficult to use the PCINA device; one due to inadequate pain relief despite the maximum IN dose i.e. 108 mcg. (This patient went on to have a intrathecal infusion of morphine and bupivacaine); one due to a fall in RR from 20 to 16 (see above); and one patient discharged themselves against medical advice the day after the first IN administration.

Discussion

Breakthrough pain continues to be a significant issue for palliative care cancer patients. What is required for breakthrough pain management is rapid onset, relatively short duration, intense analgesia.

This was an observational study that showed that IN sufentanil was of rapid onset, effective, safe and relatively user friendly in a range from 9–108 mcg (total dose). The effective dose in the majority (63%) of patients was 18 mcg

(i.e. 2 sprays) or less. As this was a novel technique and we had minimal data to guide us, we elected for an inpatient dose titration phase and to err on the side of safety, using frequent observations of RR, sedation scores and SPO_2 so that any significant adverse effects would be detected and managed early. It turned out that we had been overly cautious, and there were no significant adverse effects, and no need for any acute interventions.

The PCINA GO Medical device is similar in design to the nasal sprays used to deliver nasal decongestants, but has important safety features, that is, the exact dose delivered is regulated, plus the possibility on an in-built lock out. We elected to use a no lockout device for two reasons:

1) the dose titration phase was doctor or nurse supervised, which imposed an effective lockout of 10 mins
2) we anticipated that more than one spray would be required, and once the dose had been determined, it would have been unreasonable to impose the standard 4 min lockout instead of letting patients use the spray to alternate nostrils at 2 min intervals to achieve this dose rapidly.

The devices are 5 or 10 ml bottles that are filled with the required analgesia, usually by a pharmacist. We elected to use sufentanil, which due to its favourable pharmokinetic properties, plus the availability of a suitable commercially available solution, appeared to us to be the most promising of the currently available opioids. Sufentanil is not routinely available in Australia, but is readily obtained through the Federal Government supervised Special Access Scheme (SAS). (Drugs on this scheme have not been approved by the Therapeutic Goods Administration, but are available on a case by case basis for patients who have a life threatening illness).

Transmucosal fentanyl citrate (OTFC) ACTIQ™ was not available in Australia when our trial started, but became available with limited access towards the end. It has now been added to our Pharmaceutical Benefits Scheme (a system which subsidises high cost medications). OTFC needs to be moved between the cheek and gum for 10 min (although ~70% of the drug is leached out in the first 5 min). Streisand, *et al.*[11] showed that with OTFC devices, an effective analgesic concentration is achieved in 15 min, lasts 1–2 hrs and the bioavailability is of the order of 50%. Portenoy, *et al.* reported on a successful dose titration trial of OTFC for breakthrough pain in domiciliary palliative care patients.[12] Interestingly, no relationship was shown between the regular 24 hr opioid required or usual breakthrough dose and the OTFC dose required. It would appear however to be a better option in patients requiring a high opioid dose for adequate control of breakthrough pain. IN sufentanil at high doses (though these were very rarely needed) is pragmatically difficult. Patients are happy to use 1–4 sprays, that is, up to 36 mcgs but above this it is a bit cumbersome, and also the amount swallowed may be significant even if given over several minutes.

We acknowledge several limitations to this study. First, it is an open label observational non-blinded study, and as such potential bias in reporting of pain results, adverse effects and patient preferences are possible. Additionally, it was conducted only in inpatient palliative care units, although some patients continued the use of the medication at home. However, as explained above, these limitations were essentially unavoidable given the lack of safety data available prior to this trial. Additionally, IN sufentanil does not come pre-packaged, and therefore requires the contents of a commercially available sufentanil ampoule to be emptied into the PCINA bottle, usually in a pharmacy.

Conclusion

Breakthrough pain in palliative care continues to be a difficult area to provide effective analgesia. The results of this study show that the IN route is a practical alternative to oral, subcutaneous and intravenous administration of medication for breakthrough pain. It provides acceptable and often preferred breakthrough analgesia for many patients and most importantly, it can provide rapid pain relief. This study also showed that IN sufentanil can be used safely, with a very low incidence of adverse effects, in an inpatient palliative care population. We suggest that IN sufentanil be added to the armamentarium of medication used to treat breakthrough pain with the proviso that it requires an initial dose titration phase, similar to that recommended when using ACTIQ lozenges.

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