

Nasal fentanyl alone plus buccal midazolam: an open-label, randomised, controlled feasibility study in the dying

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ABSTRACT

Introduction Many patients want to stay at home to die. They invariably become unable to take oral medication during their terminal phase. Symptoms are usually controlled by subcutaneous medications. There have been no studies on nasal fentanyl (NF) or buccal midazolam (BM) to control symptoms in the dying.

Objective To establish how best to conduct a definitive, randomised controlled trial (RCT) to determine whether NF and BM administered by families, for patients dying at home, lead to faster and better symptom control and fewer community nursing visits than standard breakthrough medication by healthcare professionals.

Methods This open-label mixed-method feasibility RCT compared the efficacy of NF and BM by family members to standard breakthrough medication by nurses for the terminally ill in a specialist palliative care unit. Partway through the study, a third observational arm was introduced where BM alone was used. The primary outcomes were whether recruitment and randomisation were possible, assessment of withdrawal and drop-out, and whether the methods were acceptable and appropriate.

Results Administration of NF and BM was acceptable to patients and families. Both were well tolerated. We were unable to obtain quality of life data consistently but did get time period data for dose-controlled symptoms.

Conclusions Study participation in a hospice population of the dying was acceptable. The results will help guide future community study planning.

Trial registration number NCT02009306.

INTRODUCTION

People with terminal illnesses need timely symptom control and should be able

to die in their 'preferred place of care'¹ (usually home).² Dying patients are often too weak to take oral medication. The mainstay in the UK is subcutaneous infusions by syringe driver and top-up medication by subcutaneous injection.³ Family carers can be trained to give injections.⁴⁻⁶ In the UK, this is less common. Usually, when the terminally ill experience symptoms, a carer calls a community nurse for an injection. It can take hours for nurses to arrive.⁷ This is often distressing for patients and families.

In 2015, the Palliative Care and end of life care Priority Setting Partnership published results. It used surveys and a prioritisation workshop with patients, carers and professionals, to identify the top 10 unanswered research questions in palliative/end of life care. Symptom concerns, unscheduled hours and family support were given priority.⁸

There can be disquiet about injections.⁹⁻¹⁰ There are alternative preparations given more rapidly and easily—(both fast acting) nasal fentanyl (NF) and buccal midazolam (BM). Research has examined NF for breakthrough pain¹¹ and BM for seizures¹² but not in the dying. In preparation for a community randomised trial of these administration modes, we assessed study methodology.

METHODS

We started recruitment to a randomised controlled trial from December 2016 but gained approval to recruit an additional third observational arm of BM alone from October 2017. All patients could receive standard as needed medication. Hospice inpatients and carers fitting inclusion criteria were identified as possible



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participants by the clinical team. If the patient had capacity, the study was discussed with them first and then their carer. Where they lacked capacity, the study was discussed with carer only.

Abbreviated inclusion criteria:

- ▶ Hospice inpatients.
- ▶ Terminal cancer; estimated prognosis 1–2 weeks.
- ▶ Carer/family member willing to give medication and likely to be at the hospice at least 25% of the time.

Study procedures

Three patient information leaflets and consent forms were used for: (1) patients with capacity; (2) carers; and (3) carers willing to consent on behalf of patients lacking capacity. Potential participants were given information leaflets. After as much time as they wished, they were asked to sign appropriate consent forms. Patients eligible for groups A and B were randomised via telephone by the sponsoring hospital research support service:

- ▶ Group A—NF replaced subcutaneous opioids for pain and BM subcutaneous benzodiazepine for agitation. Group A could receive NF 4 hourly; up to four times daily on a titration schedule. Once effectively titrated, carers could also administer BM 4 hourly; up to four times daily.
- ▶ Group B—standard care—oral, sublingual or subcutaneous medication (antiemetics, antisecretory drugs, benzodiazepines and opioids).
- ▶ Patients eligible for group C—BM replaced subcutaneous benzodiazepine for agitation. Group C could receive BM 4 hourly; up to four times daily.

Nursing staff could administer trial medication if carers were not present or not confident.

Carers in groups A and C received Symptom Management Training Packs about symptom assessment and training on how to use trial drugs:

NF and BM—group A.

BM alone—group C.

Outcome measures

The following were collected: (1) time to adequate symptom control; (2) need for additional medication; (3) adverse events; (4) time to onset; (5) time from dose to symptom recurrence.

Symptoms were measured by the modified Palliative Care Outcome Scale—Symptom Module¹³ daily. After agreement from Dr Fliss Murtagh (then Reader and Consultant in Palliative Medicine at King's College, London), we removed the question on 'any other symptoms?' and added the anxiety question from the Integrated Palliative care Outcome Scale.

Adverse events

As a study in the terminally ill, it was expected death would be frequent. It was reported to the sponsor, but not considered a serious adverse event if, in the Chief Investigator's opinion, it was a natural conclusion to the illness. Deaths did not require immediate reporting

to the Medicines and Healthcare products Regulatory Agency or Ethics Committee.

Statistical analysis

For all quantitative outcome measures, the main aim was feasibility of intervention delivery to help design a main trial. Indicative outcomes were underpowered for statistical interpretation.

RESULTS

There were 337 hospice admissions during the study period (320 individuals). Three hundred and eight did not meet inclusion criteria. Main reasons not terminally ill; not on a high enough background opioid dose; family not present 25% of the time. Of the 29 eligible patients/carers approached, 9 declined. Of the 20 patients enrolled, 3 completed the study, 8 died and 9 withdrew (family request—4; adverse event—2; unable to titrate NF—2; discharged home—1). Of nine in arm A, one died before study drug and two withdrew because they could not be titrated on NF (ie, pain uncontrolled 30 min after 800 µg dose). All nine in arm B received symptom-relieving medication. Of the two in arm C, one did not receive study drug. There were 308 breakthrough episodes requiring medication: arm A—165; arm B—125; arm C—18. There were 85 doses of experimental drug given; 41 post-titration.

Median time from recruitment to death was 7 days; 1 patient lived 119 days. In arm A, the successful NF dose was 100 µg for 2; 200 µg for 3; 400 µg for 1. Of the three given BM (arms A and C), all responded to 2.5 mg. There were missing data for outcome measures but none for dose timing. Results are in table 1 for the six titratable patients in arm A, nine arm B and one in arm C who received trial medication. Those successfully titrated on study drugs had faster and longer lasting symptom control than standard medication.

Adverse events

There was one serious adverse event (wrong dose of study drug).

Table 1 Primary and secondary outcomes

Outcomes	Median time: min (IQR)	
	Experimental drugs post titration (arms A, C—41 episodes)	Standard drugs (arms A, B, C—223 episodes)
Primary outcomes		
Time to symptom control from when needed	20 (17.5–29.0)	30 (25.0–38.0)
Time from medication to onset of symptom control	10 (9.0–16.0)	20 (16.0–30.0)
Secondary outcome		
Time from medication to next breakthrough medication	380 (142.5–694.0)	275 (152.5–537.5)

DISCUSSION

It was possible to conduct a feasibility study in a single hospice. When we planned this study, carers administering symptom medications at home were rare. It was thought safer to conduct a feasibility study in a controlled environment. In the years, it took to finalise the protocol, secure funding and approvals; a multicentre, feasibility, community randomised trial has been conducted comparing subcutaneous medication administered by families versus healthcare professionals.¹⁴

It was expected that many admissions would be ineligible. Half of the unit's admissions go home. Often the families of those admitted are unable to provide care (or would not be present 25% of the time). Patient/family distress or likely inability to safely administer drug were issues in a few. Families approached often wanted the opportunity to give medication. A future community study would only approach terminal patients wanting to stay at home (perhaps making recruitment easier). Recruitment time was limited by a short expiry date for BM. A substantial amendment was approved for an observational arm C (BM alone as experimental drug). This led to two patients recruited and while one did not receive study medication, the other did receive symptomatic benefit. There was much missing data. We were wary of burdening patients, families and busy staff. As the study required caregivers to be present 25% of the time, we anticipated missing data for family assessments. There was much missing nursing assessment data despite research team support including training sessions and 24 hours research team advice.

The drugs were largely well tolerated. Of concern was the wrong dose of NF on three occasions by nursing staff; in one incident, four times the correct dose. We classified this as a serious adverse event. The patient was sleepier but otherwise unharmed. No errors were made by families and these incidents confirm how important training and 24 hours support would be in a potential community study. For a future community study, dose timing, number of doses used and need for rescue medication from community nurses would be the best outcome measures.

CONCLUSIONS

We hope to use lessons from this research to plan studies to investigate how best to support patients dying at home and their families. One would expect those in a specialist palliative care unit to have the most complex symptoms and families struggling to cope with home care. A future community study would likely recruit more 'normal dying' with easier to treat symptoms and families more able to help. Our study showed that even among the most complex illnesses, patients and families are happy to participate.

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Contributors PP conceived the study. AP and EH made substantial contribution to its design. AP collected most of the data. RKA was responsible for data analysis. PP is the guarantor.

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Competing interests PP and EH have in the past received financial support to attend educational events from Kyowa Kirin.

Patient consent for publication Not required.

Ethics approval The study was approved by Gloucestershire Research Support Service, the Sue Ryder Research Governance Group, the National Research Ethics Service Committee South Central – Berkshire and the MHRA. The clinical trial was registered in EudraCT, the EMEA database for clinical trials (code EUDRACT 2013-005009-30).

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Data availability statement Data are available upon request

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