An open-label, randomised controlled feasibility study to evaluate whether nasal fentanyl alone and in combination with buccal midazolam give better symptom control to dying patients when compared with standard as needed medication

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Abstract

Introduction

Many patients want to die at home and they invariably become unable to take oral medication; symptoms are usually controlled using subcutaneous drugs. There have been no studies examining the use of nasal fentanyl (NF) or buccal midazolam (BM) to control symptoms at the end of life.

Objective

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

Material and methods

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

Results

The administration of NF and BM was considered acceptable by patients and families, and both medications were well tolerated. We were unable to consistently obtain data on quality of life outcome measures but there was no missing data with regards to how long doses controlled symptoms.

Conclusions:

Participation in such a study in a hospice population was acceptable. The results will help planning of a future community study.

Introduction

When patients are dying they often become too weak to be able to take medication orally and the mainstay of treatment in the United Kingdom is subcutaneous infusions by syringe driver and top-up medication as needed by subcutaneous injection given by community nurses[1]. Out of hours, it can take several hours for a nurse to arrive[2,3]. This delay is often very distressing for families and patients.

Carers can be trained to give breakthrough medication[4-6]. There are preparations that offer an alternative to subcutaneous administration and could be given more rapidly and easily – NF and BM.

For this study we chose the preparation of BM used locally (Epistatus). We chose PecFent over other fast acting fentanyls as it has four advantages - Only two dose strengths; visible counter with audible click; ease of administration to a patient with decreased consciousness; absorption does not depend on the amount of saliva[7].

Methods

Study design

An open label, randomised, controlled feasibility study.

Study population

We recruited to an open label randomised controlled trial from December 2016:

- Group A – Experimental – NF replacing subcutaneous opioids and BM replacing subcutaneous benzodiazepine
- Group B – Standard Care – oral, sublingual or subcutaneous medication

From October 2017 we recruited to an additional third observational arm:

- Group C – Experimental – BM replacing subcutaneous benzodiazepine

Abbreviated Inclusion Criteria:

- Hospice in-patients with cancer and an estimated prognosis of 1-2 weeks.
- Carer/family member who would be willing to give study medication AND likely to be at the hospice at least 25% of the time.

Study procedures

Carers in Groups A and C received Symptom Management Training Packs including tips on symptom assessment; and training on how to use trial drugs. Experimental drugs were placed in lock boxes at patient's bedside.

In Group A patients could be given NF up to four hourly, up to four times a day using a titration schedule until they had been successfully titrated. Once an effective dose of NF had been found, carers could also administer BM up to four hourly, up to four times a day.

Patients in Group C could receive BM up to four hourly, up to four times a day as their sole experimental drug.

Nursing staff could administer trial medication if a carer was not present OR did not feel confident.

The experimental medications used in this trial were supplied free of charge by the manufacturers – PecFent – NF (Archimedes Pharma and then latterly Kyowa Kirin Ltd) and Epistatus – BM (Special Products Limited latterly called Veriton Pharma Ltd).

Results

Participant characteristics

There were 337 hospice admissions during the study period. For 308 of these admissions, the patient did not meet the inclusion criteria. Of the 29 eligible patients/carers approached, 9 declined participation.

Of the 20 patients enrolled, 3 patients completed the study, 8 patients died while in the study and 9 patients were withdrawn from the study.

Of 9 patients randomised to Arm A, 1 died before they received any study drug and 2 patients were withdrawn because they could not be titrated on NF i.e. their pain was not adequately controlled at 30 minutes after an 800mcg dose. All 9 patients allocated to Arm B received symptom relieving medication. Of the 2 in Arm C, 1 did not receive study drug.

Median time from recruitment to death was 7 days; 1 patient lived 119 days.

Results for primary and secondary outcome measures are in Table 1 for the 6 titratable patients in Arm A, the 9 patients in Arm B and the 1 patient in Arm C who received trial medication. The patients who could be successfully titrated on study drugs had faster and longer lasting control of symptoms compared with those who received standard medication.

Adverse events

There was only 1 serious adverse event – the administration of the wrong dose of study drug (in Arm A). There were no adverse events in Arm C.

Table 1: Primary and secondary outcomes

Outcomes	Median time in minutes (Interquartile range)	
	Experimental drugs post-titration (Arms A and C – 41 episodes)	Standard drugs (Arms A, B and C – 223 episodes)
Primary outcomes		
Time to symptom control from when medication needed	20 (17.5 – 29.0)	30 (25.0 – 38.0)
Time from medication needed to onset of symptom control	10 (9.0 – 16.0)	20 (16.0 – 30.0)
Secondary outcome		
Time from medication given to administration of 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. Many patients and families admitted were not eligible. The main reasons were that the patient was not thought to be dying; not taking a high enough dose of morphine (or equivalent); or the carers were not present 25% of the time.

Nine of 29 approached did not wish to participate. Qualitative interview data will be reported elsewhere.

There was much missing data. As the study only required carers to be present 25% of the time it is expected that there would be missing data with regard to carer assessment. It is disappointing that there was so much missing data with regard to nursing staff's estimation of effectiveness despite good support from the research team including training sessions from the research nurse and availability of 24 hour advice from the research team. Discussion with the nurses revealed that this was a symptom of how busy they were.

For a future community study we think that timing of doses; number of doses used; and the need for rescue medication from community nurses would be the best outcome measures.

The drugs were largely well tolerated. What was of great concern was how the wrong dose of nasal fentanyl was given on 3 occasions by nursing staff. In one incident the patient received four times the dose of nasal fentanyl they should have. We classified this as a serious adverse event. The patient was more sleepy after having the wrong dosage but was otherwise unharmed.

No errors were made by families during the study but these incidents confirm to us how important training and 24 hour support would be for families in the community participating in a similar study.

We hope to use the lessons learned to help plan further studies to investigate the best way to support patients dying at home and their families. One would expect patients in a specialist palliative care unit to have the most complex symptoms and to have families struggling to cope. A future community study would likely recruit more 'normal dying' patients with easier to treat symptoms and families more able to help them to stay at home. Even amongst the most complex, patients and families are happy to take part in such a study. There were few days of data lost due to withdrawal but there was a lot of missing data with both families and staff poor at recording how well patients responded to medication. Timings of medication were well recorded and this would seem to be a suitable outcome measure for further studies.

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Approvals/Ethics: 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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palliative, neurological and bereavement support