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

Authors: Paul Perkins1,2; Anne Parkinson2; Ralph K Akyea3; Emma Husbands1
1 Gloucestershire Hospitals NHS Foundation Trust, Cheltenham, UK
2 Sue Ryder Leckhampton Court Hospice, Cheltenham, UK
3 Division of Primary Care, University of Nottingham, Nottingham, UK

Abstract
Introduction
Many patients 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. Participating families who required a third observational arm was introduced where BM alone was used as study drug. The primary outcomes were whether recruitment and randomisation was 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 majority of the study in the United Kingdom is subcutaneous infusions by syringe driver and top-up medication as needed by subcutaneous injection given every 4 hours. It can take several hours for a nurse to arrive 1,2. This delay is often distressing for families and patients. Several hours for a nurse to arrive2,3. This delay is often distressing for families and patients.

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 midazolamide
• 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 midazolamide

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
Careers in Groups A and C received Support in 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 satisfactorily titrated. Once an effective dose of NF had been found, carers could also administer BM to 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 (Achmeads Pharma) 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 participants, 9 declined participation. Of the 20 patients enrolled, 3 patients completed the study, 8 died within 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 800mg dose. All 9 patients allocated to Arm B received symptom relieving medication. Of the 2 in Arm C, 1 did not receive study drug.

Table 1: Primary and secondary outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Experimental drugs post-titration (Arms A and C)</th>
<th>Standard drugs (Arms A, B and C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcomes</td>
<td>Time to symptom control when medication needed</td>
<td>Time from medication needed to onset of symptom control</td>
</tr>
<tr>
<td></td>
<td>20 (17.5 – 25.0)</td>
<td>20 (16.0 – 30.0)</td>
</tr>
<tr>
<td></td>
<td>10 (9.0 – 16.0)</td>
<td>20 (16.0 – 30.0)</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td>Time from medication given to administration of next breakthrough medication</td>
<td>380 (142.5 – 694.0)</td>
</tr>
<tr>
<td></td>
<td>275 (152.5 – 537.5)</td>
<td></td>
</tr>
</tbody>
</table>

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 medicines for it to be felt effective; 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 and doses of 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 there was an incident where the patient did not receive any study drug and 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.

Acknowledgements: We are grateful to the patients and families who participated in this study; and also the staff who look after our patient. We would also like to thank the following – Sarah Carruthers (Protocol Development (PD), Trial Management Group (TMG)), Beccy Day (Research Nurse); Franny Geller (PD, Randomisation, TMG), Church Road, Cheltenham, GL53 0QJ

Corresponding author: Dr Paul Perkins
Chief Medical Director – Sue Ryder AND Consultant in Palliative Medicine Gloucestershire Hospitals NHS Foundation Trust and Sue Ryder Leckhampton Court Hospice
Church Road, Cheltenham, GL53 0QJ
Tel: 01242 230199
Fax: 01242 224776
Email: paul.perkins@quirkydcan.org