Diamorphine or alfentanil for subcutaneous use in hospice inpatients?

▸▸ Opioid rotation is a common practice in palliative care in trying to balance analgesia with side effects. **Paul Perkins, Chris Foy** and **Marie Fallon** present the results of a feasibility study conducted to investigate the ability to recruit patients without renal dysfunction to a trial comparing diamorphine or alfentanil for subcutaneous use in hospice inpatients.

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Opioid rotation is commonly used when patients have intolerable opioid-related side effects.[1] How patients metabolise analgesia may affect pain relief and tolerability, with renal impairment leading to opioid metabolite accumulation.[2] In the UK, the use of diamorphine as a subcutaneous infusion is standard practice when palliative care patients are unable to take strong opioids orally. Diamorphine, an analgesic in its own right, is de-acetylated to morphine, which is also analgesic.[3] Morphine is metabolised, mainly in the liver, to two principal metabolites: morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G).[4] While M6G is an opioid agonist, M3G has negligible affinity for opioid receptors.[5] These metabolites rely on the kidneys for excretion and accumulate in patients with renal failure,[6] leading to potentially serious side effects.[7]

Guidance [2,8] advocates the use of subcutaneously administered alfentanil or fentanyl as the parenteral opioids of choice for patients with renal impairment, while recognising that there is little rigorous supporting evidence. It is believed that these opioids are likely to be better choices than diamorphine in this group of patients, as they will not lead to the accumulation of active opioid metabolites. While it is accepted practice to use these alternative opioids for patients with renal impairment, their use is not standard practice for patients with normal renal function. It would be helpful to know whether alfentanil could provide a better balance of analgesia and side effects for these patients too. Delirium is common in terminally ill patients,[9] with a prevalence as high as 80% in the last few days of life,[10] and the use of opioids is thought to be one contributing factor.[11,12]

We undertook a feasibility study to assess the ability to recruit patients without renal dysfunction to a randomised controlled trial comparing diamorphine or alfentanil for subcutaneous use in hospice inpatients (DASH).

Methods

Ethical approval for this study was provided by the Cambridge East Research Ethics Committee. Consenting inpatients in our specialist palliative care unit, who had an estimated glomerular filtration rate ≥40 ml/min/1.73 m^2 and required treatment with diamorphine via a syringe driver, were randomly assigned in an open-label fashion to either stay on diamorphine or switch to alfentanil. Daily assessments were conducted, including the Brief Pain Inventory Short Form (BPI-SF) and Memorial Delirium Assessment Scale (MDAS). The primary outcome measures for this feasibility study were: the number of patients screened; the percentage of patients eligible; the percentage of patients recruited; the percentage of patients reaching Days 3 and 7; and data completion.

Analysis

The analysis performed was largely descriptive and exploratory: changes were calculated and compared between the two groups, using Mann–Whitney U tests. IBM SPSS Statistics version 22.0 was used for these tests.

Results

Between December 2010 and June 2014, 562 hospice inpatients, who had an estimated glomerular filtration rate ≥40 ml/min/1.73 m^2 and were on, or about to be started on, a subcutaneous syringe driver, were screened for inclusion in the study. Of these, 544 did not meet the inclusion criteria (some for more than one reason) because they were:

- not on diamorphine (n=312)
- too ill to participate (n=178)
- not likely to be on syringe driver for 7 days (n=188)
- participating in another study (n=25).

This means that 24 patients (4%) were eligible for inclusion; however, six declined participation, so that 18 (3%) were recruited. Of these, nine

were randomly assigned to stay on diamorphine and nine to switch to alfentanil. Data were collected for 56/63 days for patients on diamorphine and 48/63 days for those on alfentanil. All 18 patients lived to Day 3.

Patients were withdrawn from the study if they became too unwell or died during the seven-day study period; this was the case for two patients on diamorphine (one unwell, one died) and four on alfentanil (two unwell, two died). Median survival from Day 0 was 25 days (range 3–50) for patients on diamorphine and 24 days (range 4–786) for those on alfentanil. Other results are presented in Table 1. Patients randomly assigned to alfentanil were receiving higher doses of opioids pre-randomisation than those in the diamorphine arm. During the study, patients on diamorphine increased their background opioid dose by an average of 9% and those on alfentanil by an average of 27% (not statistically significant).

Three patients (one on alfentanil and two on diamorphine) developed delirium during the seven-day study according to the MDAS cut-off score of 13.

The most common adverse event observed was worsening pain when patients were switched to alfentanil.

Table I. Summary of results

	Diamorphine	Alfentanil
Total number of patients	9	9
Male	2	2
Age range (years)	50–85	52–74
Average age (years)	65.3	58.4
Mean diamorphine dose at Day 0 (mg/24 h range)	21 (5–40)	73 (30–220)
Mean syringe driver dose at Day 1 (mg/24 h range)	21 (5–40)	7 (2–22)
Regular adjuvant medications (number of patients – some patients on more than one medication)		
Paracetamol	3	4
NSAID	2	2
Gabapentin	1	3
Dexamethasone	1	2
Baclofen	0	1
None	4	3
MDAS; median score (n)		
Baseline	3 (9)	3 (9)
Day 3	3.5 (8)	2 (7)
Day 7	3 (7)	0 (5)
BPI-SF; mean severity score (median)		
Baseline	3	3.5
Day 3	2.5	4.25
Day 7	3.25	3.75
BPI-SF; interference (median)		
Baseline	6.0	7.3
Day 3	4.3	4.4
Day 7	2.3	5.3
Number of breakthrough doses/patient-day during the study from Day 1 onwards	1.4	2.9
Mean syringe driver dose last evaluable day (range)	22.8 (5–40)	8.9 (3–25)

BPI-SF: Brief Pain Inventory Short Form; MDAS: Memorial Delirium Assessment Scale; NSAID: non-steroidal anti-inflammatory drug

Discussion

The objective of this study was to evaluate whether a randomised controlled trial using this methodology could be performed to compare diamorphine and alfentanil given by subcutaneous infusion for the management of pain in hospice inpatients. We have shown that such a study is not practicable. It took three years and six months to recruit 18 patients. As a specialist palliative care unit, we are referred patients with the most complex symptoms. By the time patients were referred to the hospice, many had already been on opioids and rotated to oxycodone, or were already on alfentanil. Some had already developed renal impairment or were too ill or confused to participate.

We chose not to recruit delirious patients, in contrast to the study by Morita *et al*,[13] in which the investigators recruited 21 patients with morphine-induced delirium and rotated them to fentanyl. Delirium was no longer present by Day 7 in 18 of these patients. There are, however, interesting parallels with our study. In the study by Morita *et al*, patients who were switched to fentanyl required an increase in their opioid dose of 42%. The authors argued that switching allowed maximal dose titration. In our study, patients who continued on diamorphine required a dose increase of 9% and those on alfentanil an increase of 27%, although this difference was not statistically significant.

In our study, patients in the alfentanil arm were on higher doses of subcutaneous diamorphine pre-recruitment than those in the diamorphine arm (Day 0 dose: 73 mg/24 h versus 21 mg/24 h), while they also received more adjuvant medications and required more doses of breakthrough analgesia during the study, so it is possible that patients in the alfentanil arm simply had worse pain from the time of enrolment.

The most common adverse event in the study was less effective pain control when patients were switched to alfentanil. Few differences were

observed between the two groups in BPI-SF and MDAS scores after Day 0. Patients on alfentanil had worse pain scores but lower delirium scores.

The results of this feasibility study demonstrate serious problems with recruitment, with no evidence that alfentanil is at least as effective as diamorphine in this patient group. The results, therefore, provide little or no support for a definitive randomised controlled trial of alfentanil against diamorphine in the hospice setting ■

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Declaration of interest
The authors declare that there are no conflicts of interest.

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Key points

- Opioid rotation is commonly used to try and achieve a better balance between analgesia and side effects.
- While alfentanil is commonly used subcutaneously to provide pain relief for palliative care patients with renal failure, there is little evidence for its use in patients with normal renal function, and it would be useful to know if it could provide a better balance of analgesia and side effects than diamorphine in those patients.
- The results of this study provide little or no support for a definitive randomised controlled trial of alfentanil against diamorphine in the hospice setting.