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Use of parecoxib by continuous subcutaneous infusion for cancer pain in a hospice population

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ABSTRACT

Objectives To characterise the use of the parenteral non-steroidal anti-inflammatory drug parecoxib when given by continuous subcutaneous infusion (CSCI) in a hospice population. Clinical experience suggests parecoxib CSCI may be of benefit in this population, but empirical evidence in relation to its safety and efficacy is lacking.

Methods Retrospective chart review of patients with a cancer diagnosis receiving parecoxib CSCI from 2008 to 2013 at the Marie Curie Hospice, Belfast. Data were collected on treatment regime, tolerability and, in patients receiving at least 7 days treatment, baseline opioid dose and changes in pain scores or opioid rescue medication requirements.

Results Parecoxib CSCI was initiated in 80 patients with a mean administration of 17.9 days (median 11, range 1–94). When used for a period of 7 days, there was a statistically significant reduction in pain scores (p=0.002) and in the number of rescue opioid doses required (p=0.001), but no statistically significant opioid-sparing effect (p=0.222). It was generally well tolerated, although gastrointestinal, renal adverse effects and local site irritation were reported.

Conclusions Parecoxib may have a valuable place in the management of cancer pain, especially towards the end of life when oral administration is no longer possible and CSCI administration is relied on. Further studies into the efficacy and tolerability of parecoxib CSCI are merited.

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BACKGROUND

Non-steroidal anti-inflammatory drugs (NSAIDs) are non-opioid analgesics recommended for regular use in the WHO analgesic ladder for mild to moderate pain.[1] NSAIDs vary in their adverse effect profile with those showing selective inhibition of cyclo-oxygenase-2 (COX-2) displaying less gastrointestinal adverse effects.[2] Parecoxib, a prodrug of valdecoxib, is an injectable selective COX-2 inhibitor marketed in the UK as Dynastat Injection by Pfizer Limited. It is licensed for the short-term treatment of postoperative pain in adults by the intramuscular or intravenous routes.[3] It has been used extensively by continuous subcutaneous infusion (CSCI) in palliative care in Northern Ireland; however, evidence for its safety and efficacy by this route is lacking.

AIM OF THE STUDY

This study aims to:

1. retrospectively record the usage and tolerability of CSCI parecoxib in patients with advanced cancer at Marie Curie Hospice, Belfast
2. investigate if CSCI parecoxib was associated with a reduction in pain scores at any time, or when given for minimum 7 days: (1) reduction in background opioid dose and (2) reduction in frequency of opioid rescue medication doses.

METHOD

All inpatients prescribed CSCI parecoxib from 2008 to 2013 were identified from pharmacy records. Patients with a non-cancer diagnosis or admitted already receiving parecoxib CSCI were excluded. A retrospective chart review was undertaken to collect data from the medical notes on patient demographics, medical history, baseline medication, parecoxib dose, duration, diluent, volume of infusion and adverse effects. For patients receiving at least 7 days of CSCI parecoxib, background opioid (converted to oral morphine equivalence using regional conversion tables) and rescue opioid use were recorded, and a one-way repeated measures analysis of variance was applied. Where recorded, pain scores (0–10 Numerical Pain Rating Scale) were

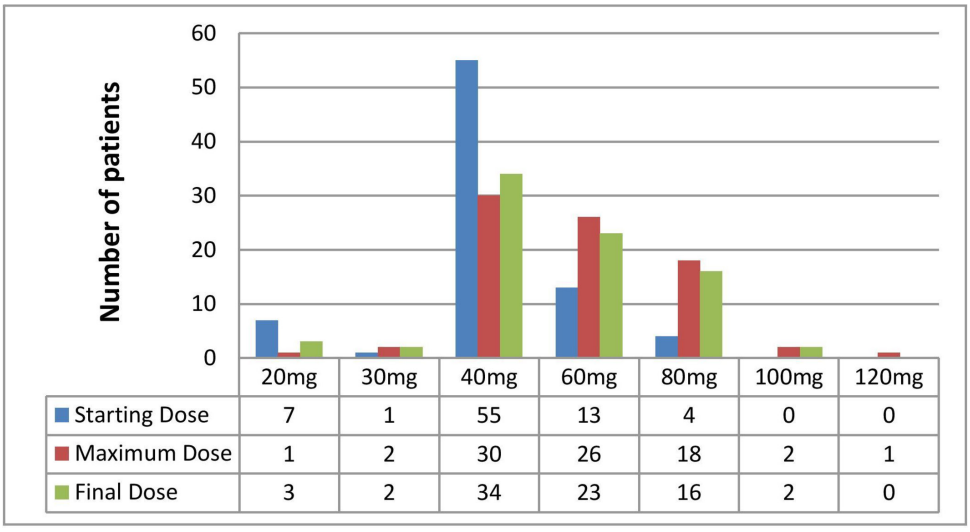

Figure 1 Parecoxib CSCI dosing. The median starting dose was 40 mg and the majority of patients had a maximum and final dose of 60 mg or less.

documented, and a Wilcoxon signed-rank test was used. As this study was a service evaluation, ethical approval was not sought; however, the study methodology was reviewed and approved by the Marie Curie Hospice Belfast Research Group.

RESULTS

Eighty patients were identified, 46 males (57%) and 34 females (43%). Mean age was 62 years (range 36–79 years, SD 10.9). The most common cancer diagnoses were lung (20%), colorectal (13.8%), prostate (11.3%) and breast (10%).

The indications were metastatic bone pain 44/80 (55%); non-malignant pain 13/80 (16.3%); mixed pain including metastatic bone with another pain 10/80 (12.6%); visceral pain 5/80 (6.3%) and unknown 8/80 (10%). Twenty-eight (35%) patients switched to parecoxib CSCI from various oral NSAIDs, 3/80 from ketorolac or diclofenac CSCI and 5/80 from topical NSAIDs. Sixty-two patients (77.5%) received CSCI parecoxib for at least 7 days. Gastroprotection was coprescribed in 74/80 patients, most commonly a proton pump inhibitor (72/80).

Dose and administration (see figure 1)

After initial dosing, 36 (45%) patients had a dose increase, 35 (43.8%) no dose change, 5 (6.3%) a decrease and 4 (5%) an increase then subsequent decrease. Mean duration of treatment was 17.9 days (median 11, range 1-94). Parecoxib was administered alone apart from two patients where it was combined with dexamethasone 500 µg. Sodium chloride 0.9% was the diluent in 78/80 patients. Water for injection was used in 2/80, but both were subsequently switched to sodium chloride 0.9% due to local site irritation. Mean total volume was 11.9 mL (range 9–22 mL, SD 2.6). Patients who developed local site reactions had a mean volume of 11.7 mL versus 12 mL for those not experiencing such effects. All diluted solutions were visually compatible. Thirty-seven patients continued parecoxib CSCI until death in the hospice with 19/80 (24%) discharged on parecoxib and the clinical decision made to stop in the remainder. Reasons for stopping included adverse effects (12/80), switching to oral NSAID (7/80) and lack of efficacy (5/80).

Adverse effects

Forty per cent (32/80) of patients had at least one adverse effect recorded in the medical notes (table 1). The maximum number of adverse effects in a single patient was two. One patient reported both dyspepsia and haematemesis.

Opioid dose

Fifty patients (63%) were coadministered CSCI opioids, 20/80 (25%) regular oral opioids, 4/80 (5%) transdermal opioids, one intrathecal opioid and 5% (4/80) received no regular opioid. Of the 62/80 patients receiving at least 7 days CSCI parecoxib and concurrent regular opioid medication, the mean oral

Table 1 Adverse effects reported in medical notes (n=80)

Adverse effect	Incidence	Resulted in parecoxib discontinuation
Local site reactions	15	1
Reduction in renal function	11	3
Dyspepsia	8	2
Haematemesis	2	2
Malaena	2	2
GI perforation	1	1
Rash	1	1
Itch	1	–
Total	41	12

GI, gastrointestinal.

morphine equivalent (MME) background opioid dose was 258 mg on day 1 and 240 mg on day 7. This reduction was not statistically significant (p=0.222). Fifty-eight of the 62 patients also received rescue opioid doses, and there was a statistically significant reduction in mean number of rescue opioid doses per day from 1.88 on day 1 to 1.22 on days 6 and 7 (p=0.001).

Pain scores

Only 16/80 (20%) of patients had pain scores recorded on day 1 and at least one other day from days 2–7. Median pain scores reduced from 7 on day 1 (IQR 5–8) to 4 on the 'final day pain score' (IQR 2–6), which was a statistically significant change (Z=−3.154, p=0.002).

DISCUSSION

Parecoxib is licensed for the short-term treatment of postoperative pain by intravenous or intramuscular injection[3] and has been given by daily subcutaneous injection for cancer pain.[4] In our study of CSCI use, bone pain was the most frequent documented indication, involving 54/72 (75%) patients. This is in keeping with recorded use of diclofenac and ketorolac CSCI,[5–8] the other parenteral NSAIDS commonly used within palliative care. The licenced maximum daily dose of parecoxib is 80 mg. In our study, the most common starting dose was 40 mg and 62/80 (78%) had a final CSCI dose of 60 mg or less. Three patients received above 80 mg daily, although local practice now dictates a maximum of 80 mg/day, including 'as required' use, is generally adhered to.

Studies on postoperative parecoxib and a meta-analysis of NSAIDs in cancer pain both demonstrated an opioid-sparing effect not seen in our study.[9 10] However, with over a third of our patients previously taking oral or parenteral NSAID, this may reflect one of the challenges with our retrospective methodology.

While over one-third of adverse effects were local site reactions, the overall incidence (18.8%) is comparable with other CSCI studies.[11] Such comparisons are challenging due to different reporting methods, with the rate for CSCI ketorolac site reactions in the literature ranging from 0% to 70%.[5–7] Simple non-drug measures such as using different giving sets or changing the administration site more frequently have been recommended to reduce site reaction incidence.[11 12] The mean total volume was 11.9 mL but, as a result of the study, our standard practice has changed. We now dilute parecoxib CSCI to 22 mL using sodium chloride 0.9%. This maximises dilution and avoids using water for injection (which is hypotonic) to reduce local site reactions.[12]

After discounting site reactions, the majority of adverse effects 24/26 (92%) were renal or gastrointestinal, both commonly recognised with NSAID use.[13 14] These did not appear to be dose related. Most patients were coprescribed gastroprotection (recommended as standard practice for patients at risk of gastrointestinal ulceration, including the elderly[15]) and in the two cases of haematemesis, one had their gastroprotective agent stopped due to diarrhoea while the other, with a history of gastrointestinal ulceration, had been taking oral meloxicam prior to parecoxib CSCI. The case of gastrointestinal perforation was managed conservatively with a short hospital admission. None of the gastrointestinal adverse effects identified were life threatening or required ongoing treatment. These results are lower than recorded in the largest study of CSCI ketorolac where four cases of gastrointestinal bleeding out of 36 patients were reported, despite receiving gastroprotection.[7] However, the small numbers and methodology do not allow us to compare the two studies with any validity. Another study comparing intravenous ketorolac and parecoxib with placebo in healthy older adults found no incidence of gastrointestinal ulceration with parecoxib or placebo after endoscopy, while in those receiving intravenous ketorolac nearly a quarter had developed a gastrointestinal ulcer after 5 days.[16]

Of the 66 patients who had a repeat estimated glomerular filtration rate (eGFR) performed after starting parecoxib CSCI, 11 had a reduction in renal function, defined as eGFR below 60 or any reduction from baseline (where eGFR already less than 60). Of these, one had pre-existing impairment, four had already been taking an NSAID and three were on other nephrotoxic medicines. There were no cases where eGFR fell below 30, and only 3/11 patients had parecoxib CSCI discontinued as a precaution. Of note it is recognised that reduction in renal function in patients with advanced cancer towards the end of life is not uncommon.[17]

Parecoxib and valdecoxib, in common with other NSAIDs, are associated with an increased risk of cardiovascular events, after as early as 30 days treatment in patients who have undergone coronary artery bypass grafting.[18] They are also associated with unpredictable but serious skin reactions which, combined with the cardiovascular risk, led to the withdrawal of valdecoxib from the European market in 2005.[19] No cardiovascular events were noted in our study, and the rash and itch seen were both self-limiting and possibly unrelated to parecoxib; however, this study was not sufficiently powered to accurately detect these effects. For all adverse effects, individual patient risk factors and likely duration of CSCI parecoxib should be considered. Towards the end of life, prescribers may feel the benefits of symptom control outweigh the potential risks of treatment.

STRENGTHS AND WEAKNESSES

The drawbacks of using retrospective chart reviews are well documented,[20] and the challenges of locating and interpreting information from medical notes reduced

the study population. However, with the financial, ethical and logistical difficulties of prospective study design in palliative care noted, retrospective methodology is frequently used in hospice settings,[21] and all apart from one of the current studies on CSCI NSAIDs use this methodology.

With only 20% of patients having a sufficient number of pain scores recorded to calculate benefit, a much larger sample would be needed to confirm this. While no significant reduction in MME was noted, the reduction in frequency of opioid rescue doses, which has been validated as an appropriate measure in pain research,[22] was statistically significant. The clinical significance of this (1.88 in day 1 to 1.22 in days 6 and 7) is difficult to confirm due to other confounding patient-related factors.

Given the complexity of prescribing and disease trajectory of this patient population, the lack of a comparator group makes it difficult to reach definitive conclusions about CSCI parecoxib regarding efficacy and adverse effects. Other factors such as altering the regular opioid dose, coprescribing adjuvants and non-pharmacological interventions were also not recorded. However, with no published information available on CSCI parecoxib, this study is a first step to building up knowledge of this drug when used in a specialist palliative care population for cancer pain.

CONCLUSIONS

This retrospective study demonstrated that parecoxib CSCI was both efficacious and generally well tolerated. Parecoxib could have a valuable place in the management of cancer pain, particularly bone pain and towards the end of life when oral administration is no longer possible. However, patient selection and assessment remains important to minimise significant adverse effects and the ongoing balance between risk and benefit in this population continues to require considered clinical approach.

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Contributors All authors were involved in the design of the study, data analysis and interpretation. PA collected the data and drafted the article. PW and NKM critically revised the article. All authors gave final approval of the version to be published.

Competing interests None declared.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

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Data sharing statement The original anonymised data for the 80 patients is available on request from the main author. This includes patient demographics, diagnosis, baseline medicines, parecoxib dosing regime, pain scores (if recorded), side effects, oral morphine equivalent doses, breakthrough opioids given and duration of treatment.

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