The combination of parecoxib and propacetamol reduces opioid consumption and hypoxemic episodes following unilateral hip arthroplasty

M.N. Essex,¹ F. Camu,² P. Bhadra Brown,¹ R. Cheung¹

¹Pfizer Inc, New York, NY, USA; ²Department of Anesthesiology, University of Brussels, Brussels, Belgium

INTRODUCTION

- Multimodal analgesic approaches for postoperative pain aim to eliminate pain, reduce opioid use, and prevent opioid-related side effects.^{1,2}
- Respiratory depression is a potentially fatal side effect of opioid use.^{3,4}
- The use of combinations of nonopioid analgesics for postoperative pain may lead to additive or synergistic effects, including on opioid consumption, but data are sparse.^{5,6}
- The opioid-sparing efficacy of parecoxib, a cyclooxygenase-2 selective inhibitor, and propacetamol, the pro-drug of paracetamol, have been demonstrated in a variety of settings.⁷⁻¹¹
- Recently, a multicentre, double-blind, randomised, noninferiority, placebo-controlled trial tested the efficacy and safety of combined parecoxib and propacetamol as well as each drug alone after unilateral total hip arthroplasty (THA).¹²
- This trial assessed the opioid-sparing capacity of parecoxib, propacetamol, and parecoxib + propacetamol, but the effects of each drug alone or in combination on respiratory depression were not extensively studied.
- The aim of this exploratory post hoc analysis was to evaluate the effect of parecoxib, propacetamol, and combined treatment on the frequency of hypoxemic episodes in unilateral THA patients, and to examine factors affecting the occurrence of hypoxemia.

METHODS

- The original clinical trial was conducted in 18 centres across 5 countries in accordance with Good Clinical Practice Guidelines, the Declaration of Helsinki, and the institutional review board and/or independent ethics committee of the participating centres. Each patient provided written informed consent prior to entering the study.¹²
- Men and women aged ≥18 years were included if they were undergoing routine unilateral THA performed under spinal anaesthesia and were expected to experience moderate or severe postoperative pain in the absence of postoperative analgesia.
- Patients undergoing a revision to a previous hip replacement or emergency hip replacement were excluded.
- Patients were randomised to receive 1 of 4 intravenous treatments: parecoxib 40 mg twice daily (BID) plus propacetamol placebo 4 times daily (QID) (PAR group); propacetamol 2 g QID plus parecoxib placebo BID (PROP group); parecoxib 40 mg BID + propacetamol 2 g QID (PAR+PROP group); or parecoxib placebo BID plus propacetamol placebo QID (PBO group). Patients and investigators were blinded to treatment.
- The first dose of study medication was administered after the last surgical stitch (time 0). The duration of study treatment was 48 h.
- Subjects who required additional pain medication were given morphine via bolus and/or patient-controlled analgesia. Dose, date, and time of administration were recorded, and the cumulative amount of morphine administered during the study was captured.
- Opioid distress was measured using the Opioid-Related Symptom Distress Scale (OR-SDS)¹³ at 24 and 48 h.
- Where available, peripheral blood oxygen saturation levels (SpO₂) were measured, using pulse oximetry in patients not receiving supplemental oxygen after surgery.
- Hypoxemia was defined as SpO₂ <90%.
- The times and oximeter readings of all hypoxemic episodes were recorded.
- The effect of patient age, time since initiating study treatment, and cumulative morphine dose at the time of the hypoxemic episode on the occurrence of hypoxemia were examined.
 - All treatment groups were pooled because too few hypoxemic episodes occurred to analyse each treatment group separately.
- Differences in the proportion of patients with hypoxemia were determined using a Cochran-Mantel-Haenszel test adjusted for centre. Correlation coefficients were determined between the occurrence of hypoxemic episodes and patient age, time since initiating study treatment, and cumulative morphine dose at the time of the hypoxemic episode.

RESULTS

- 253 patients were randomised; 72 received parecoxib, 71 propacetamol, 72 parecoxib + propacetamol, and 38 placebo.¹²
- At baseline, treatment groups were not significantly different ($p>0.05$) with respect to age, race/ethnic origin, gender, vital signs, height, or weight.¹²
- Fewer patients in the parecoxib + propacetamol group ($n=4$, 5.6%) had a history of respiratory problems at baseline compared with parecoxib ($n=9$, 12.5%), propacetamol ($n=9$, 12.7%), or placebo ($n=7$, 18.4%).
- No significant differences among treatment groups were observed in surgical procedure (left or right hip), duration of surgery, time to first dose of study medication from start of surgery, and duration of anaesthesia.¹²

Opioid Consumption and Opioid Distress

- Parecoxib, propacetamol, and parecoxib + propacetamol significantly reduced morphine consumption vs. placebo at 24 and 48 h after surgery (all $p<0.01$) (Figure 1).¹²
 - The greatest reduction was seen with parecoxib + propacetamol at both time points.
 - Non-inferiority of parecoxib to parecoxib + propacetamol was not demonstrated, with the combination showing greater analgesic efficacy than parecoxib alone.
- At 24 h, parecoxib + propacetamol and parecoxib alone, but not propacetamol alone, significantly reduced opioid symptom distress vs. placebo as assessed by the OR-SDS (both $p<0.05$) (Figure 1).¹²
 - Parecoxib + propacetamol also significantly reduced OR-SDS total score at 48 h ($p=0.005$).¹²

Figure 1. Effect of active treatment on morphine consumption and opioid symptom distress vs. placebo at 24 and 48 h after surgery

Occurrence of Hypoxemic Episodes

- 29 hypoxemic episodes were reported; the fewest number of episodes were reported with parecoxib + propacetamol treatment (Figure 2).
- 17 patients reported hypoxemia (Figure 2). Only 1 patient suffered from a respiratory problem at baseline (placebo group).
- A significantly smaller proportion of patients in the parecoxib + propacetamol group had hypoxemic episodes vs. placebo ($p<0.05$).
- A smaller proportion of patients had hypoxemic episodes in the parecoxib and propacetamol groups vs. placebo, but the differences were not statistically significant.
- Figures 3, 4, and 5 show the effect of patient age, time since initiating study treatment, and cumulative morphine dose at the time of the hypoxemic episode on the occurrence of hypoxemia.
- No significant correlation between hypoxemic episodes and patient age ($r=-0.13$), time since initiating study treatment ($r=0.23$), or cumulative morphine dose at the time of the episode ($r=0.18$) was observed.

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Figure 2. No. of hypoxemic episodes and proportion of patients reporting hypoxemia by treatment group

Figure 3. Effect of patient age on the occurrence of hypoxemic episodes

Figure 4. Effect of time since the patients initiated study treatment on the occurrence of hypoxemic episodes

Figure 5. Effect of the patients' cumulative morphine dose at the time of the episode on the occurrence of hypoxemic episodes

CONCLUSIONS

- Parecoxib and propacetamol alone or in combination significantly reduced morphine consumption vs. placebo in patients following unilateral THA.¹²
- Parecoxib + propacetamol also significantly improved opioid symptom distress vs. placebo.¹²
- Hypoxemic episodes were infrequent in all treatment groups, but the fewest occurred with parecoxib + propacetamol; the proportion of patients with hypoxemia in the parecoxib + propacetamol group was significantly smaller vs. placebo.
- There appears to be a direct relationship between morphine consumption and hypoxemic episodes:
 - Parecoxib + propacetamol caused the greatest reduction in morphine consumption and opioid symptom distress and was associated with the fewest episodes of hypoxemia in the smallest proportion of patients.
- The link between hypoxemia and morphine consumption appears to be more complex for parecoxib and propacetamol alone.
 - More hypoxemic episodes were reported in the parecoxib group than in the propacetamol group, despite the fact that parecoxib reduced morphine consumption more than propacetamol.
- Patient age, time since initiating study treatment, and cumulative morphine dose at the time of the hypoxemic episode did not appear to affect the occurrence of hypoxemic episodes.
- By preventing hypoxemic events, nonopioid analgesics may reduce the potentially fatal effects of opioid-related respiratory depression.

DISCLOSURES

This study was sponsored by Pfizer. FC was the lead investigator of the original clinical trial and has acted as consultant to pharmaceutical companies and health authorities. He declares no conflict of interest with the present work. MNE, PBB, and RC are full-time employees of Pfizer and have stock options in Pfizer. Medical writing support was provided by David Cope, PhD, of Engage Scientific Solutions and funded by Pfizer.

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