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Pain

PAIN

Randomized clinical trial of dexketoprofen/tramadol 25 mg/75 mg in moderate-to-severe pain after total hip arthroplasty

H. J. McQuay[1,*], R. A. Moore[2], A. Berta[3], O. Gainutdinovs[4], B. Fülesdi[5], N. Porvaneckas[6], S. Petronis[7], M. Mitkovic[8], L. Bucsi[9], L. Samson[10], V. Zegunis[11], M. L. Ankin[12], M. Bertolotti[13], B. Pizà-Vallespir[14], S. Cuadripani[14], M. P. Contini[13] and A. Nizzardo[13]

[1]Balliol College, University of Oxford, Oxford, UK, [2]Pain Research & Nuffield Division of Anaesthetics, University of Oxford, The Churchill, Oxford OX1 3BJ, UK, [3]Department of Orthopaedics, Uzsoki Hospital, Budapest, Hungary, [4]Department of Joint Surgery, Hospital of Traumatology and Orthopaedics, Riga, Latvia, [5]Department of Anesthesiology and Intensive Care, University of Debrecen, Debrecen, Hungary, [6]Department of Traumatology and Orthopaedics, Republican Vilnius University Hospital, Vilnius, Lithuania, [7]Department of Traumatology and Orthopaedics, Riga's 2nd Hospital, Riga, Latvia, [8]Clinic for Orthopaedics and Traumatology, Clinical Center Nis, University of Nis, Nis, Serbia, [9]Department of Orthopaedics, St George University Teaching Hospital, Szekesfehervar, Hungary, [10]Department of Orthopaedics, MÁV Hospital, Szolnok, Hungary, [11]Department of Traumatology, Klaipeda University Hospital, Klaipeda, Lithuania, [12]Orthopedic & Trauma Center, Kiev Regional Clinical Hospital, Kiev, Ukraine, [13]Clinical Research, Menarini Ricerche S.p.A. – Menarini Group, Florence, Italy, and [14]Clinical Research, Laboratorios Menarini S.A. – Menarini Group, Badalona, Spain

*Corresponding author. E-mail: henrymcquay@gmail.com

Abstract

Background: The aim was to evaluate the analgesic efficacy and safety of the dexketoprofen/tramadol 25 mg/75 mg fixed-dose combination *vs* dexketoprofen (25 mg) and tramadol (100 mg) in moderate-to-severe acute pain after total hip arthroplasty.
Methods: This was a randomized, double-blind, parallel-group study in patients experiencing pain of at least moderate intensity on the day after surgery, compared with placebo at first administration to validate the pain model. The study drug was administered orally every 8 h throughout a 5 day period. Rescue medication, metamizole 500 mg, was available during the treatment period. The evaluation of efficacy was based on patient assessments of pain intensity and pain relief. The primary end point was the mean sum of the pain intensity difference values throughout the first 8 h ($SPID_8$).
Results: Overall, 641 patients, mean age 62 (range 29–80) yr, were analysed; mean (SD) values of $SPID_8$ were 247 (157) for dexketoprofen/tramadol, 209 (155) for dexketoprofen, 205 (146) for tramadol, and 151 (159) for placebo. The primary analysis confirmed the superiority of the combination over dexketoprofen 25 mg (P=0.019; 95% confidence interval 6.4–73) and tramadol 100 mg (P=0.012; 95% confidence interval 9.5–76). The single components were superior to placebo (P<0.05), confirming model

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sensitivity. Most secondary analyses supported the superiority of the combination. The incidence of adverse drug reactions was low and similar among active treatment groups.
Conclusions: The efficacy results confirmed the superiority of dexketoprofen/tramadol over its single components, even at higher doses (tramadol), with a safety profile fully in line with that previously known for these agents in monotherapy.
Clinical trial registration: EudraCT 2012-004548-31 (https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-004548-31);
ClinicalTrials.gov NCT01902134 (https://www.clinicaltrials.gov/ct2/show/NCT01902134?term=NCT01902134&rank=1).

Key words: analgesics; arthroplasty, replacement, hip; dexketoprofen trometamol; pain, postoperative; tramadol

Editor's key points

- This study focuses on the efficacy of combining a non-steroidal anti-inflammatory drug with tramadol.
- Combining dexketoprofen and tramadol was effective, with a reduction in required tramadol dose.
- Less rescue medication was used when dexketoprofen and tramadol were combined.
- Adverse events were predictable from the known safety profile, although further studies are needed.

Despite the great variety of analgesics available, acute pain management is still often inadequate.[1–3] Possible causes include the subjective nature of pain, incorrect diagnosis, or fear of adverse drug reactions (ADRs).[4]

Combining different analgesics that act by different mechanisms (multimodal analgesia) to enhance clinical outcome is a common strategy in pain management. Combinations do well in single-dose analgesic studies,[5] and there is a strong argument for additivity of drug-specific benefits.[6] Some of the potential benefits of combinations include broader spectrum of action, greater efficacy, better compliance, complimentary pharmacokinetic profile, and better efficacy-to-safety ratio.[7]

Dexketoprofen, the active chiral form of ketoprofen, is effective in acute pain[8] in a wide variety of conditions,[9] with an onset of analgesic effect within 30 min.[10] Tramadol is a widely used opioid of proven efficacy in combination with paracetamol.[11] The combination of dexketoprofen/tramadol is expected to result in additive analgesia, thus allowing a decrease in the required doses of the single agents (particularly tramadol), and with the benefit of quick onset (typical of dexketoprofen) and long duration (tramadol) of the analgesic effect. A previous dose-finding study allowed for the selection of dexketoprofen/tramadol 25 mg/75 mg as the optimal combination of doses to be evaluated further.[12]

The present study was designed to demonstrate the superior efficacy of dexketoprofen/tramadol 25 mg/75 mg over the individual components (tramadol given at a higher dose) in moderate-to-severe acute pain after total hip arthroplasty and to evaluate its safety and tolerability.

Methods

Ethical approval

The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki, was approved by all concerned Ethics committees, and was registered with EudraCT (2012-004548-31) and ClinicalTrials.gov (NCT01902134). Written informed consent was obtained from all patients. It was a multicentre, randomized, double-blind, double-dummy, placebo- and active-controlled, parallel-group, phase III study encompassing a single-dose phase (SDP) and a multiple-dose phase (MDP). It was conducted at 37 study sites in 10 countries (Czech Republic, Germany, Hungary, Latvia, Lithuania, Poland, Serbia, Spain, Taiwan, and Ukraine) between May 2013 and February 2014.

Patient population

The patients were men and women aged 18–80 yr, undergoing standard primary unilateral total hip arthroplasty because of osteoarthritis (excluding osteoarthritis secondary to systemic or metabolic diseases, trauma, or infections) and experiencing pain at rest of at least moderate intensity on the day after surgery. Women participating in the study had to be either of non-childbearing potential or willing to use a highly effective contraceptive method.

Patients with known allergy or contraindication to the study drugs or rescue medication (RM) were excluded from the study, as were patients using and not able to stop analgesics other than those specified in the protocol. Medications whose concomitant use with the study drugs or RM were not advisable or might confound the study results were restricted during pre-specified time frames (related to drug characteristics such as half-life). Restricted medications included monoamine oxidase inhibitors, antiepileptics, antipsychotics, serotonin reuptake inhibitors, tricyclic antidepressants, lithium, methotrexate, antibacterial sulphonamides, and ondansetron. Anticoagulants, thrombolytics, and antiplatelet agents were also restricted, with the exception of standard perioperative thromboprophylaxis and cardioprophylactic use of low doses of aspirin (≤325 mg). Patients with moderate to severe renal dysfunction, severe hepatic or severe cardiac dysfunction, history of gastrointestinal disorders, bleeding disorders, severe asthma, and epilepsy were excluded from participation in the study (according to the investigator's judgement after assessment of the medical history, physical examination, vital signs, ECG, and laboratory safety tests at screening). Patients with a history of drug or alcohol abuse, chronic opioid users (recent use of major opioids or tramadol for more than 1 week), and pregnant or breast-feeding women were also excluded.

Conduct of the study

Patients were enrolled at each site by the investigators according to inclusion and exclusion criteria. The surgical procedure (including the anaesthetic regimen) was performed in accordance with the current site medical practice. Postoperative analgesia consisted of i.v. or i.m. morphine or other short-acting opioids. The day after surgery, 1 or 2 h after cessation of postoperative analgesia (depending on route of administration), and provided that patients were capable of taking oral medications, patients who experienced pain of at least moderate intensity [defined as pain intensity visual analog scale (PI-VAS) ≥40] were eligible to be randomized.