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Tramadol/Dexketoprofen (TRAM/DKP) oral fixed dose combination is superior to tramadol/paracetamol in moderate-to-severe acute pain: a randomized, double-blind, placebo and active-controlled, parallel group trial (DAVID study)

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Abstract

Objectives: The aim of this study was to compare the analgesic efficacy and safety of oral tramadol hydrochloride 75mg/dexketoprofen 25mg (TRAM/DKP) versus oral tramadol hydrochloride 75mg/paracetamol 650mg (TRAM/paracetamol) in moderate to severe pain following extraction of impacted lower third molars (a well-established analgesic model for moderate-to-severe pain assessment).

Design: Multicentre, randomized, double-blind, double-dummy, parallel-group, placebo and active-controlled, single dose, phase IIIb study including three treatment arms.

Setting: 18 centres including hospital clinics and dental surgeries in five European countries (Hungary, Italy, Poland, Spain and United Kingdom).

Participants: Healthy adult patients (>18 years of age) scheduled to undergo surgical extraction of at least one fully or partially impacted lower third molar requiring bone manipulation were included in the trial. A total of 654 patients were randomized to receive study treatment and 653 were included in the analysis: TRAM/DKP 260 patients (152 female, 108 male); TRAM/paracetamol 262 patients (158 female, 104 male), placebo 131 patients (78 female, 53 male).

Interventions: Surgery was performed under local anaesthetic using 2% lidocaine (with 1:80.000 epinephrine) up to a total volume of 5.4 ml per molar. No sedation was permitted. After surgery, patients rated pain intensity (PI) using a 11-Numerical Rating Scale (NRS) ranging from 0 (no pain) to 10 (worst pain). Participants experiencing moderate to severe pain (≥ 4) within 4 hours after surgery were randomized with a 2:2:1 ratio to a single oral dose of TRAM/DKP 75/25mg, TRAM/paracetamol 75/650mg or placebo. During the eight-hour post-dose assessment period, oral ibuprofen (400mg) was permitted as rescue medication (RM) up to a maximum of two tablets at a minimum interval of four hours.

Main outcome measures: Evaluation of efficacy was based on data entered by patients in an eDiary. Analgesia and pain were recorded using the following measures: pain relief (PAR) on a 5-point verbal rating scale (VRS) (0='no relief', 1='a little (perceptible) relief', 2='some (meaningful) relief', 3='lot of relief', 4='complete relief') at the pre-defined post-dose time points t15min, t30min, t1h, t1.5h, t2h, t4h, t6h and t8h; and PI on the 11-point NRS at t0 and at the same pre-defined post-dose time points. The onset of analgesia was documented using the double stopwatch method over a two-hour period. The primary endpoint was total pain relief over 6 hours (TOTPAR6).

Results: The combination TRAM/DKP was superior to TRAM/paracetamol and placebo at the primary endpoint TOTPAR6 ($p < 0.0001$). Mean TOTPAR6 in the TRAM/DKP group was 13 (6.97), while mean (SD) values in the active control and placebo groups were 9.1 (7.65) and 1.9 (3.89), respectively. Superiority of TRAM/DKP over active comparator and placebo was observed at all secondary endpoint. Incidence of adverse events was comparable between active groups.

Conclusions: Tramadol hydrochloride/dexketoprofen trometamol (75/25mg) is an effective analgesic and superior to TRAM/paracetamol (75/650mg) in relieving moderate-to-severe acute pain. TRAM/DKP exerts faster onset of action, greater and durable analgesia, together with a favourable safety profile. This head-to-head comparison provides robust evidence that TRAM/DKP (75/25mg) is a valuable tool in controlling moderate-to-severe pain offering effective multimodal analgesia.

Trial registration: EU Clinical Trials Register (EudraCT 2015-004152-22) and at Clinicaltrials.gov (NCT02777970).

What this paper adds

- It is difficult to obtain an effective analgesia in patients with moderate to severe pain with a single drug and analgesics are commonly combined to optimise pain control.
- Multimodal analgesia is beneficial in treating acute and chronic pain but *ad hoc* combinations of analgesics are often used empirically without knowing the mechanism of interaction and/or the best dose ratio of the analgesics to be combined to achieve optimal efficacy and safety.
- The fixed-dose combination of dexketoprofen (25 mg) and tramadol (75 mg) (DKP/TRAM FDC) provides a comprehensive multimodal approach for moderate-to-severe acute pain, thanks to the central analgesic effect, peripheral analgesic action, and anti-inflammatory activity.
- The efficacy of the dexketoprofen/tramadol 25mg/75mg fixed-dose combination in the management of moderate to severe acute pain has been already confirmed in phase II and phase III clinical trials.
- This study has shown that tramadol hydrochloride/dexketoprofen trometamol 75/25mg oral fixed combination is effective and superior over tramadol hydrochloride/paracetamol 75/650mg in relieving moderate-to-severe acute pain.
- Pain is the most common symptom for which patients seek medical attention. Our results show dexketoprofen/tramadol fixed-dose combination may play an important role in the management of moderate-to-severe acute pain.

Introduction

The majority of patients with moderate-to-severe acute postoperative pain report inadequate pain relief.¹ This is in spite of the well-known and published negative impact on clinical outcomes including delay of functional recovery after surgery, increased risk of post-surgical complications, progression from acute pain to chronic/persistent pain and reduced quality of life. It is also associated with increased visits to healthcare professionals and hospitalizations with consequent increases in overall health care costs.¹⁻⁴ It is difficult to attain adequate pain relief with monotherapy and multimodal analgesia is now accepted as the cornerstone in the effective treatment of pain. Combining analgesics from different classes with diverse mechanisms of action and potential synergistic effects means that a wider spectrum of pain can be covered and lower doses of single drug components can be administered. This approach, based on the combination of analgesic agents with different but complementary mechanisms of action, enhances efficacy and minimizes the risk of adverse events.⁵

Dexketoprofen, a non-steroidal anti-inflammatory drug (NSAID), is a well-known inhibitor of Cyclooxygenase (COX-1 and COX-2) and appears to be as effective as the double dose of the racemic ketoprofen, but with a faster onset of analgesia. It has proven analgesic and anti-inflammatory efficacy in a wide spectrum of acute pain syndromes. It has a fast onset of action and a favourable pharmacokinetics profile with rapid distribution.

Dexketoprofen trometamol has an increased bioavailability compared to the free drug, as the salt produces a more rapid dissolution and absorption, (t_{max} between 0.25–0.75 h), thus ensuring rapid pain relief which is crucial for the effective management of acute pain.⁶⁻⁸ Dexketoprofen trometamol is an effective analgesic to relieve pain in the acute symptomatic period and has been shown to be beneficial in a wide range of clinical conditions. Dexketoprofen efficacy is complemented by its favourable safety profile. Recent clinical data show that it has an adverse event profile similar to that of the new generation NSAIDs.⁸

Tramadol, a μ -opioid receptor agonist, noradrenaline and serotonin re-uptake inhibitor, is a central-acting analgesic.^{9,10} Its opioid and non-opioid mechanisms are thought to act synergistically on descending inhibitory pathways in the central nervous system, resulting in the modulation of second order neurons in the spinal cord. Moreover, tramadol inhibition of monoamine re-uptake augments the chemical signal of the descending pain inhibitory pathways, while decreasing the ascending pain impulse. Tramadol analgesic efficacy is complemented by a long duration of action (half-life around 6h) and by a safety profile that favours tramadol over other opioids.⁸

Recent clinical evidence demonstrated that the oral fixed drug combination of tramadol hydrochloride 75mg with dexketoprofen 25mg (TRAM/DKP) is an effective analgesic for the control of moderate-to-severe acute pain.^{8,11-14} The fixed oral combination of TRAM/DKP offers a number of important advantages including: proven efficacy and tolerability with a 25% overall reduction in the opioid dosage, improved compliance, as well as a convenient mode of administration. A fixed oral combination TRAM/DKP (75/25mg) (film-coated tablet) has been registered and released for commercial use in Europe.¹⁵

Direct comparisons of newly released drugs with older agents are rarely performed in clinical trials, although this kind of evidence is valuable to improve appropriateness of pharmacotherapy in clinical practice.¹⁶ The lack of data regarding direct comparison between analgesics can make it difficult for clinicians to determine the optimal therapeutic option.¹⁷ In order to provide a meaningful comparison of the analgesic capabilities of TRAM/DKP fixed combination versus oral tramadol hydrochloride 75mg /paracetamol 650mg (TRAM/paracetamol), a head-to-head clinical trial was necessary.

We therefore designed a phase IIIb trial investigating TRAM/DKP for the oral treatment of moderate-to-severe acute pain following removal of impacted lower third molars (Dexketoprofen Analgesic eVolution wIth tramaDol, DAVID). The objective of the study was

to compare the analgesic efficacy and safety of the fixed oral combination TRAM/DKP (75/25mg) versus TRAM/paracetamol (75/650mg) in postoperative pain following extraction of impacted lower third molars, an established experimental model for moderate-to-severe acute pain assessment. The model is widely accepted and has a proven record of assay sensitivity to compare efficacy, including onset of analgesic action, in head-to-head trials.^{18,19} Efficacy in the dental model is also highly predictive of efficacy in other pain settings.²⁰

Methods

The study, approved by all the concerned Competent Authorities and Ethics Committees, (Sponsor Code DEX-TRA-06) was registered at the EU Clinical Trials Register (EudraCT 2015-004152-22) and at Clinicaltrials.gov (NCT02777970). It was performed at 18 centres in five European countries (Hungary, Italy, Poland, Spain and United Kingdom) and was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. All participating patients provided written informed consent. The clinical phase of the study started in April 2016 and was concluded in February 2017.

Patients

Healthy adult patients (>18 years of age) scheduled to undergo surgical extraction of at least one fully or partially impacted lower third molar requiring bone manipulation were included in the trial. Criteria for randomization included postoperative pain of moderate to severe intensity (Numerical Rating Scale, NRS ≥ 4) within a 4-hour time lapse after the completion of the surgery.

Pregnant or breastfeeding women or women of childbearing potential not using adequate contraception were excluded from the study. The following conditions did not permit participation in the study: known allergy or hypersensitivity to study treatments, rescue medication (RM) or any other NSAIDs except those permitted in the study protocol, opioids and acetyl salicylic acid; history of peptic ulcer, gastrointestinal disorders induced by NSAIDs

or gastrointestinal bleeding; Crohn's disease or ulcerative colitis; severe asthma; moderate to severe renal dysfunction; severe hepatic dysfunction or cardiac dysfunction; active bleeding or coagulation disorders; history of, or current epilepsy; history of drug or alcohol abuse; as well as history/presence of any illness or condition that, in the opinion of the Investigator, might pose a risk to the patient or confound the efficacy and safety results of the study. Patients who had received any investigational drug or participated in any other clinical trials within the previous four weeks were also excluded. Patients who had taken, sedatives, hypnotic agents or analgesics within 12 hours before surgery and eight hours post-dose (or five days prior to the surgery day in case of COX-2 inhibitors) were not considered eligible. Moreover, subjects under chronic opioid treatment, or using and not suitable for withdrawing, within 48 hours (or five half-lives, whichever the longer pre-surgery), drugs posing a risk to the patient and for 24 hours post-dose, were also not enrolled. Lastly, patients were excluded if any surgical complication occurred that, in the opinion of the investigator, would interfere with the study procedures or assessments.

Study design

This was a multicentre, randomized, double-blind, double-dummy, parallel-group, placebo and active-controlled, single dose, phase IIIb study including three treatment arms.

Participation in the study lasted for approximately three weeks for each patient and was made up of: a screening period, (within two weeks before randomization), including the pre-surgery procedures to be completed at least one day prior to surgery and ending within the 4-hours qualification post-surgery; randomization and treatment administration (day 1, t0) followed by a 8-hour assessment period during which patients recorded efficacy data using an electronic diary (eDiary) both at site (up to t2h) and out of site (up to t8h); followed by an end of study visit (6±1 days after randomization).

Surgery was performed under local anaesthetic using 2% lidocaine (with 1:80.000 epinephrine) up to a total volume of 5.4 ml per molar. No sedation was permitted. After surgery, patients rated pain intensity (PI) using a 11-Numerical Rating Scale (NRS) ranging from 0 (no pain) to 10 (worst pain).^{21,22} Participants experiencing moderate to severe pain (≥ 4) within 4 hours after surgery were randomized with a 2:2:1 ratio to a single oral dose of TRAM/DKP 75/25mg, TRAM/paracetamol 75/650mg or placebo. During the eight-hour post-dose assessment period, oral ibuprofen (400mg) was permitted as rescue medication (RM) up to a maximum of two tablets at a minimum interval of four hours.

Randomisation and masking

Randomization was performed through Interactive Voice/Web Response System (IVRS/IWRS) according to a computer-generated randomization sequence. Participants, healthcare providers, medical monitors, other personnel involved in the conduction of the trial, data collectors and biometricians were unaware of the treatment that participants were receiving. Double-blind conditions were ensured by the application of double dummy technique.

Sample size calculation

A sample size of 230 patients per active arm was considered adequate to demonstrate the non-inferiority of TRAM/DKP compared to TRAM/paracetamol assuming a non-inferiority margin of 20%, a power of 80% and an overall significance level of 2.5% (1-side). The mean TOTPAR6 for TRAM/paracetamol is assumed equal to 7.4 (SD 6.30). 115 patients in the placebo arm were considered sufficient to demonstrate the superiority of both TRAM/paracetamol and TRAM/DKP versus placebo for model sensitivity. Assuming about 10% of major protocol violators and 20% of screening failure rate a total of 640 patients needed to be randomized.

Efficacy evaluation

Evaluation of efficacy was based on data entered by patients in eDiary. Analgesia and pain were recorded by using the following measures: pain relief (PAR) on a 5-point verbal rating scale (VRS) (0='no relief', 1='a little (perceptible) relief', 2='some (meaningful) relief', 3='lot of relief', 4='complete relief')^{20,23} at the pre-defined post-dose time points t15min, t30min, t1h, t1.5h, t2h, t4h, t6h and t8h; and PI on the 11-point NRS^{21,22,24} at t0 and at the same pre-defined post-dose time points.

The onset of analgesia was documented using the double stopwatch method over a two-hour period post dose. Following treatment, two stopwatches were automatically activated in the eDiary. Subjects were instructed to stop the first stopwatch when they felt 'first perceptible' pain relief (FPPAR, i.e. at the moment they first felt any pain relief whatsoever) and the second when they experienced a 'meaningful' pain relief (MPAR, i.e. when the relief from pain became meaningful to them). The FPPAR and MPAR could be alternatively defined by using the time-point when PAR is assessed as 1 and 2, respectively, in case the stopwatch was not used or used after the recording of the PAR equal to 1 or 2. Furthermore, an overall assessment of the study medication was reported through patient global evaluation (PGE) on a 5-point VRS (1=poor, 2=fair, 3=good, 4=very good, 5=excellent) at the end of the 8h assessment period, or immediately before the RM intake.²⁰ The time between treatment administration and first intake of RM, and percentage of patients requiring RM were also evaluated. After first intake of RM, patients were no longer required to use the eDiary, including the stopwatch functionality.

Primary and secondary endpoints

The primary efficacy endpoint was total pain relief (TOTPAR), calculated as the weighted sum of the PAR scores measured according to a 5-point VRS, over 6 hours post-dose (TOTPAR6). Secondary efficacy endpoints included the time course of mean PAR and PI

scores over 8h; TOTPAR over 2, 4 and 8 hours post-dose and the percentage of maximum calculated TOTPAR (% max TOTPAR) over 2, 4, 6 and 8h; sum of pain intensity difference (SPID) and the percentage of maximum calculated SPID (% max SPID) over 2, 4, 6 and 8h; percentage of responders in terms of pain relief or pain intensity reduction, namely subjects who achieved at least 50% of max TOTPAR or at least 30% of PI reduction versus baseline at prespecified time points over the 8 h, respectively; time to FPPAR; time to confirmed FPPAR (i.e. time to FPPAR if confirmed by experiencing MPAR) and time to MPAR; percentage of patients who achieved FPPAR, confirmed FPPAR and MPAR within 30 minutes, 1h and 2h; PGE at 8h or whenever the patient used RM; time of first intake of RM since study drug intake; percentage of patients using RM at 2, 4, 6 or 8h.

Safety

Safety evaluation was based on the incidence, seriousness, intensity and causal relationship of treatment-emergent adverse events (AEs). AEs were assessed throughout the study. Safety was evaluated by the assessment of clinically significant changes post-dose versus the baseline in the physical examination, vital signs (VS; blood pressure and heart rate), and laboratory safety tests (haematology, biochemistry and urinalysis). Any patient who prematurely withdrew after having received study medication was encouraged to undergo the end of study visit.

Statistical analysis

The primary efficacy variable was analysed on the per protocol (PP) and intention-to-treat (ITT) populations to assess the non-inferiority hypothesis using analysis of covariance (ANCOVA) with one-sided significance level of 2.5% for testing the differences in treatment efficacy, as quantified by TOTPAR₆, between TRAM/DKP and TRAM/paracetamol. The ANCOVA model included terms of treatment and the baseline PI (NRS) as covariates. In case of non-inferiority being confirmed, the superiority of TRAM/DKP versus TRAM/paracetamol

was tested on the ITT population. Superiority of TRAM/DKP and TRAM/paracetamol versus placebo was evaluated in order to confirm the model sensitivity on the ITT population. Non-inferiority hypothesis was satisfied if the lower limit of the confidence interval for the estimated difference between TRAM/DKP and TRAM/paracetamol was greater than a non-inferiority margin of 20% of the estimated mean of TRAM/paracetamol.

Secondary efficacy analysis SPID6 was analysed for non-inferiority with the possibility to switch for superiority analogously to the primary efficacy variable. All the other secondary efficacy variables were descriptively analysed and tested for the superiority of TRAM/DKP, when applicable, through *ad hoc* inferential analyses, as follows: NRS-PI, SPID (excluded SPID6), %max SPID, TOTPAR (excluded TOTPAR6), %max TOTPAR (continuous variables) were analysed by ANCOVA model as for the primary efficacy variable; VRS-PAR and PGE (categorical variables) were analysed by Wilcoxon rank-sum test; percentage of patients who required RM, and percentage of patients achieving at least 50% max TOTPAR or 30% of PI reduction, with confirmed FPPAR or MPAR were tested using a Chi²-Test. Time to use RM, time to FPPAR, confirmed FPPAR and MPAR were assessed using a Log-rank test. All analyses were performed in SAS v.9.3 (SAS Institute Inc., Cary, NC, USA).

Imputation

The method of last observation carried forward (LOCF) was applied among patients who missed more than one consecutive data input; otherwise the missing value was replaced by the mean of the two non-missing data collected respectively before and after the missing one. This procedure was applied to all efficacy outcomes. If PI was missed at t0 the value recorded during qualification procedure was used as a baseline. After RM intake, PI returned to its baseline (t0) level and PAR to zero (“no relief”) for all subsequent time points (i.e. baseline observation carried forward, BOCF).

Safety analysis

Adverse events were coded using the MedDRA dictionary. The incidence of each treatment emergent adverse event (TEAE) was summarized by system organ class (SOC), preferred term (PT) and treatment. Clinically significant abnormal findings in VS and physical examination were listed by treatment. Safety variables were analysed by descriptive statistics and were run on the safety population.

Definition of analysis population

The ITT population consisted of all patients randomized; safety population of all patients who received study drug as per protocol (PP) of all patients of the ITT who did not experience relevant protocol deviation related to efficacy endpoints of primary interest.

Patient Involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no specific plans to disseminate the results of the research to study participants or the relevant patient community beyond the usual channels of publication.

Role of the funding source

The study sponsor (Menarini Group) contributed to the study design, data analysis, and manuscript preparation. MH confirms that he had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 792 patients screened, 654 were randomized and received study treatment, one patient was excluded from any analysis being <18 years old (**Figure 1, Table 1**). The safety

population comprised 653 patients as did the ITT group. Patients were enrolled from hospital clinics and dental surgeries in five European countries (**Table 2**). Efficacy analyses for non-inferiority were performed on the PP population, including a total of 620 randomized patients as 33 participants were excluded due to major protocol deviations related to efficacy endpoints of primary interest. Patients' assignment to the different analysis populations occurred before the study blind was broken. One patient in the TRAM/paracetamol arm was lost at follow-up and did not attend end of study visit (**Figure 1**). Demography and baseline characteristics of different treatment groups were comparable (**Table 3**). The mean (SD) age was 26.8 (7.48) years (range 18–52) in TRAM/DKP, 27.1 (8.13) years (range 18–63) in TRAM/Paracetamol; 26.5(7.67) years (18–59) in placebo arm. Percentages of women were 58.5% in TRAM/DKP, 60.3% in TRAM/Paracetamol and 59.5% in placebo arm (**Table 3**). Patients reported mean (SD) PI values at baseline of 5.7 (1.36); 5.5 (1.34) and 5.6 (1.30) in the TRAM/DKP, TRAM/Paracetamol and placebo arm, respectively (**Table 3**).

Efficacy results

Primary endpoint

Overall, the combination TRAM/DKP showed the greatest sustained analgesia during the 6-hour post dose period as demonstrated by the TOTPAR6 primary endpoint, compared with the TRAM/paracetamol and placebo groups. Since non-inferiority was confirmed, the ITT population was used to perform superiority analyses on the primary endpoint, as pre-specified. The mean (SD) TOTPAR6 reported by patients in the TRAM/DKP group was 13 (7.0), while those in TRAM/Paracetamol and placebo groups were 9.2 (7.6) and 1.9 (3.9), respectively, demonstrating that the combination TRAM/DKP was statistically superior ($p < 0.0001$) to TRAM/paracetamol (**Table 4 and Figure 2**). The results of the analysis conducted on ITT population were consistent with those conducted on the PP, therefore the model sensitivity was confirmed.

Secondary endpoints

The time course of the mean PAR and PI scores showed that TRAM/DKP provided a more rapid onset of action compared to TRAM/paracetamol as differences were statistically significant already 30 minutes post dose. Furthermore, patients in the TRAM/DKP arm constantly had greater analgesia and lower pain intensity, in a statistically and clinically significant fashion, at each pre-specified time points until 6 hours after drug intake, in comparison to those in the comparator arm. (**Figures 3 and 4**). In addition, the PI analysis with repeated measures indicated superiority of the combination TRAM/DKP in comparison to TRAM/paracetamol during the overall 8h period of assessment ($p=0.0009$). The superiority of TRAM/DKP was also confirmed by mean values of the main secondary efficacy variable SPID6 (**Table 4**). Analysis of summary efficacy measures including TOTPAR_{2, 4 and 8}; SPID_{2, 4 and 8}; % max TOTPAR over 2, 4, 6 and 8h; % max SPID over 2, 4, 6 and 8h provided further confirmation of the superiority of TRAM/DKP versus TRAM/paracetamol ($p<0.0001$) (**Table 4, Figures 2 and 5**). Regarding percentage of responders (patients achieving at least 50% of maxTOTPAR), the best results were detected in patients treated with TRAM/DKP, who were considered responders: 71.2%, 2h and at 4h, 60.4% at 6h and 47.7% at 8h. While responders in the TRAM/paracetamol group were 44.3%, 43.1%, 38.5% and 35.5% at 2h, at 4h, at 6h and at 8h, respectively ($p<0.01$ for each time point) (**Table 5**). In addition, when responders were defined as subjects who achieved at least 30% of PI reduction versus baseline, the best results were observed with TRAM/DKP versus TRAM/paracetamol at 2h, 4h and 6h ($p<0.01$) (**Table 5, Figure 6**).

The onset of analgesia, evaluated with the double stopwatch method, was significantly faster in the TRAM/DKP group in comparison to TRAM/paracetamol group considering all the relevant secondary endpoints (FPPAR, Confirmed FPPAR and MPAR) measured within different time-periods (30 minutes, 1 hour and 2 hours post-dose). Significantly more patients in the TRAM/DKP group reported a confirmed FPPAR compared with patients in the

TRAM/paracetamol group: 76.9% vs 60.3% at 30 min, 90.0% vs 72.5% at 1 h, and 90.4% vs 72.9% at 2h ($p<0.0001$) (**Table 6, Figure 7**). The median (95% CI) times to confirmed FPPAR and MPAR after single dose of TRAM/DKP were 22 (18-24) and 42 (33-45) minutes, respectively; while the ones in the TRAM/paracetamol group were 27 (23-27) and 57 (49-57) minutes, respectively. Log-rank test between TRAM/DKP and active comparator showed a statistically significant difference ($p<0.0001$) (**Figures 8 and 9**). PGE data also showed a better performance of the combination containing dexketoprofen and tramadol over the comparator. Significantly more patients in TRAM/DKP arm (80.8%) rated the study medication as “good”, “very good” or “excellent”, than that in the TRAM/paracetamol (56.6%) and placebo (15.3%) groups (**Table 7, Figures 10 and 11**).

RM was required by significantly fewer patients in the TRAM/DKP group (7.7% within 2h; 14.6% within 4h; 33.8% within 6h) than in the TRAM/paracetamol group (20.6% within 2h; 36.3% within 4h; 45.8% within 6h) ($p<0.01$). The majority of patients randomized to placebo took RM (73.3% within 2h; 82.4% within 4h; 87.8% within 6h). Patients in TRAM/paracetamol group used RM more quickly than patients in TRAM/DKP group ($p=0.0373$). (**Figures 12 and 13**).

Safety

Overall, 52 patients (8.0%) experienced one or more adverse drug reactions (92 ADRs in total) but none of the ADRs were considered to be serious (**Table 8**). No clinically relevant differences were identified in ADRs incidences between treatment groups. Overall, the most common ADRs were: vomiting (3.8%), nausea (3.2%), dizziness (2.8%) and somnolence (1.8%) (**Table 9**). No deaths or other significant ADRs occurred. There were no clinically relevant changes in the vital signs or physical examination versus baseline. Overall, TRAM/DKP was safe and well tolerated, presenting a safety and tolerability profile fully in line with that observed in previous clinical experience.

Discussion

This study provided solid evidence showing that TRAM/DKP provides an effective analgesia for the control of moderate-to-severe pain in the postsurgical context, and is superior to TRAM/paracetamol in terms of rapidity of onset and intensity of analgesia. Statistically and clinically significant superiority of TRAM/DKP over TRAM/paracetamol was demonstrated with an overall consistency not only at the primary endpoint (i.e. TOTPAR6), but also at all different outcome measures adopted in the study. Study participants receiving TRAM/DKP combination reported lower pain scores already at the 30-minute time-point after drug administration. Fast action is an important feature for an analgesic intended to be used in the treatment of acute pain.²⁵ The earlier onset of analgesic efficacy with TRAM/DKP compared with TRAM/paracetamol may be attributable to the rapid and high bioavailability of dexketoprofen,^{25,26} that favours the rapid onset of action of the combination. Better analgesic efficacy was maintained consistently over the entire observation period, confirming the sustained analgesic action observed in previous clinical trials assessing efficacy following third molar extraction, abdominal hysterectomy and total hip arthroplasty.¹¹⁻¹³ The greater analgesic efficacy of TRAM/DKP results from the balanced and synergistic combination of peripheral and central analgesia, complemented with an anti-inflammatory action.¹² The combination TRAM/paracetamol is substantially lacking in anti-inflammatory activity, as paracetamol only inhibits the synthesis of prostaglandins in the central nervous system and peripherally blocks pain impulse generation, but unlike NSAIDs, is not a peripheral COX inhibitor.^{27,28} It can be hypothesized that this difference could have contributed to the observed reduced analgesic efficacy.

The two combinations showed clinically comparable safety profiles. Gastrointestinal disorders including abdominal discomfort, diarrhoea, nausea and vomiting were reported with similar frequencies between the two groups of patients who received active intervention.

Adverse reactions regarding the nervous system disorders were also observed in a similar proportion in both arms, although a trend towards improved tolerability could be detected in patients receiving TRAM/DKP, as compared to patients treated with TRAM/paracetamol.

The experimental dental pain model, as widely demonstrated, provides evidence being highly predictive of efficacy applicable to other acute pain settings.²⁰

Therefore, the results of this head-to-head trial can guide physicians in choosing the adequate analgesic medication to optimize clinical outcomes in the treatment of a wide range of acute pain. This is particularly true in a moment in which there is a clear tendency to abandon the early treatment with strong opioids, in patients suffering from acute moderate-to-severe pain.

Results of the present trial reinforce the clinical benefit of TRAM/DKP that emerged in the whole developmental clinical programme of this fixed combination that involved some 1,900 patients with moderate-to-severe acute pain assessed using well-established human models of acute visceral and somatic moderate-to-severe pain.¹¹⁻¹³

Conclusion

This study has confirmed that tramadol hydrochloride/dexketoprofen trometamol 75/25mg oral fixed combination is effective and superior over tramadol hydrochloride/paracetamol 75/650mg in relieving moderate-to-severe acute pain. Tramadol hydrochloride/dexketoprofen trometamol 75/25mg oral fixed combination shows faster onset of effect, greater and durable analgesia, together with a favourable safety profile. The rapid onset of analgesic effect of dexketoprofen, with its anti-inflammatory activity, associated to the sustained action of tramadol, makes this combination a valuable tool to achieve multimodal analgesia.

Declaration of interests

MH reports personal fees as a consultant for educational symposia by Menarini Group. CGE reports personal fees from Menarini Group, outside the submitted work. TD reports grants from Menarini Group, during the conduct of the study; grants and personal fees from Institute Biochimique SA, outside the submitted work. AM, SM, EG, ZTB, GV declare no conflict of interest. We attest that we have obtained appropriate permissions and paid any required fees for use of copyright protected materials

Data sharing

The relevant anonymised patient level data are available on reasonable request from the authors.

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