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REVIEW

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Combination analgesia in 2005—a rational approach: focus on paracetamol–tramadol

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Abstract A multimodal (or balanced) approach to anaesthesia is a familiar concept that offers important benefits in the management of both acute and chronic pain. Rational combinations of analgesic agents with different mechanisms of action can achieve improved efficacy and/or tolerability and safety compared with equianalgesic doses of the individual drugs. Combining different agents also enhances efficacy in complex pain states that involve multiple causes. Combinations of paracetamol plus a weak opioid agent are widely used. One such combination, paracetamol plus tramadol, exploits the well-established complementary pharmacokinetics and mechanisms of action of these two drugs. This combination has demonstrated genuine synergy in animal studies and also combines paracetamol's rapid onset of efficacy with tramadol's prolonged analgesic effect. Numerous studies have confirmed the efficacy and tolerability of paracetamol plus tramadol in both acute and chronic pain. As a single-dose treatment for acute post-operative pain, this combination delivers rapid and sustained pain relief that is greater than either agent alone. There is also extensive evidence for efficacy in the long-term management of chronic pain conditions, including osteoarthritis, low back pain and fibromyalgia. In the setting of chronic pain, paracetamol plus tramadol has shown sustained efficacy, safety and tolerability for up to 2 years without the development of tolerance. The efficacy of this combination has been demonstrated as well in respect to reduction of pain intensity and, more importantly, with regard to improvement of function and quality of life and the reduction of disability. Comparative trials have shown that paracetamol plus tramadol has comparable efficacy to paracetamol plus codeine, but with reduced somnolence and constipation compared with the codeine combination. The paracetamol plus tramadol combination is also free of organ toxicity associated with selective and non-selective non-steroidal anti-inflammatory drugs. Hence, paracetamol plus tramadol offers an effective and well-tolerated alternative to anti-inflammatory drugs or other paracetamol plus weak opioid combinations.

Keywords Atypical centrally acting analgesic · Dose-sparing effect · Multimodal analgesia · Opioid · Paracetamol plus tramadol · Synergistic effect

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Introduction

It is difficult to achieve effective pain control using a single treatment, for several reasons. Most analgesics cannot be prescribed at unlimited doses due to the ceiling of efficacy and/or safety and tolerability concerns, such as liver damage (paracetamol), gastrointestinal and cardiovascular risks [both non-selective and cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drugs (NSAIDs)], or sedation, constipation and other effects of opioid agonists [1–3]. Combining drugs from different classes offers effective analgesia at reduced doses of individual agents, which may reduce the severity of dose-related adverse events [4, 5]. Another limitation of single-agent analgesia is that many patients experience pain due to multiple causes. It is very unlikely that any single therapy will be able to target every pain mechanism for these patients, so it is logical to combine drugs with different mechanisms of action. This approach offers increased efficacy due to additive or synergistic effects without increasing the dose. The ideal combination regimen would both enhance analgesic efficacy and reduce side effects compared with either treatment alone.

The concept in anaesthesia is familiar, where "multimodal" or "balanced" anaesthesia has been widely used for many years now [6]. The concept has also recently been transferred to pain medicine; combining different analgesic modalities, such as opioid drugs with local anaesthetic, combinations of local anaesthetics or paracetamol with morphine, has demonstrated improved efficacy compared with monotherapy [7–12]. There are some similarities between the

challenge presented by perioperative analgesia and chronic pain management because adverse effects are a particular concern in both indications. In perioperative analgesia, there is a need for powerful analgesia for severe acute pain, and a multimodal approach provides increased efficacy without increased severity of adverse effects. Chronic moderate-to-severe pain often requires the effective control of pain involving multiple pain pathways, but safety and tolerability become a particular concern in long-term treatment.

A number of analgesic drug combinations have been tested for the management of post-operative pain, including paracetamol with morphine or weak opioids, such as tramadol or codeine, and paracetamol with NSAIDs [12–16]. The combination of paracetamol with a weak opioid is a well-established step in the treatment of pain. Several such combinations are available, including paracetamol plus codeine, paracetamol plus dextropropoxyphene (discontinued in the UK due to safety concerns and lack of efficacy) [17, 18] and paracetamol plus tramadol. This paper will review data on the combination of paracetamol plus tramadol.

Paracetamol plus tramadol

Paracetamol plus tramadol is a rational combination because both the mechanism of action and the pharmacokinetics of these agents are complementary. In vivo studies in mice have shown that paracetamol and tramadol produce genuine synergy over a range of doses when the two treatments are used together [19]. The clinically used combination of paracetamol 325 mg plus tramadol 37.5 mg (Zaldiar) utilises a fixed-dose ratio (8.7:1) that falls within this range of synergy. In addition, paracetamol and tramadol offer complementary pharmacokinetic profiles. Paracetamol acts quickly, with an onset of efficacy about 20 min after dosing, but pain relief peaks rapidly and declines thereafter [20]. In contrast, tramadol has an onset of efficacy at about 50 min after dosing, followed by a relative plateau of efficacy that declines very slowly over time [20]. A meta-analysis of dental pain studies including more than 1,000 patients demonstrated that the combination of paracetamol plus tramadol had the same rapid onset of efficacy as paracetamol alone (17 and 18 min, respectively), but that this efficacy was sustained for several hours (Fig. 1) [20]. In the same analysis, ibuprofen had an onset of efficacy of 34 min. The median time to re-medication was more than 5 h for both ibuprofen and paracetamol plus tramadol.

The combination of paracetamol plus tramadol also has a favourable safety profile, with no organ toxicity at licensed doses (including a lack of gastrointestinal, renal and cardiovascular effects), no effect on platelets and no immunosuppression. The reduced dose of paracetamol compared with monotherapy also minimises the risk of liver toxicity associated with high doses of paracetamol [21–24].

Numerous studies have confirmed that paracetamol plus tramadol offers improved efficacy in clinical use compared with either agent alone, and with no increase in the severity of adverse effects. Clinical experience with this combination includes post-operative, sub-acute and chronic low back pain, fibromyalgia, osteoarthritis flare pain and chronic osteoarthritis pain.

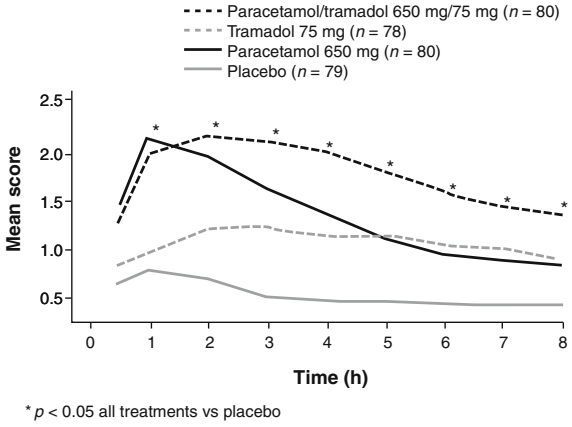

Fig. 1 Complementary pharmacokinetics of paracetamol plus tramadol. Figure adapted from Medve et al. [20]. Reproduced with permission from the American Dental Society of Anesthesiology

Paracetamol plus tramadol is efficacious in acute pain

A meta-analysis of five studies in dental pain and two studies in post-surgical pain has demonstrated that paracetamol plus tramadol is more effective than either agent alone (Fig. 2). Paracetamol plus tramadol had significantly lower (better) numbers needed to treat (NNTs) than the components alone. The NNTs to achieve 50% pain relief and relative benefit over a 6-h period were 2.6 for paracetamol 650 mg plus tramadol 75 mg, and 9.9 for tramadol 75 mg and 3.6 for paracetamol 650 mg [25]. Across all five dental pain studies analysed, 8% of patients withdrew for lack of efficacy or early re-medication on paracetamol 650 mg plus tramadol 75 mg, compared with 12% on ibuprofen, 9% on paracetamol 650 mg alone, 23% on tramadol 75 mg and 36% on placebo [25]. There was no increase in toxicity using combined therapy compared with tramadol alone. Almost all adverse effects on paracetamol

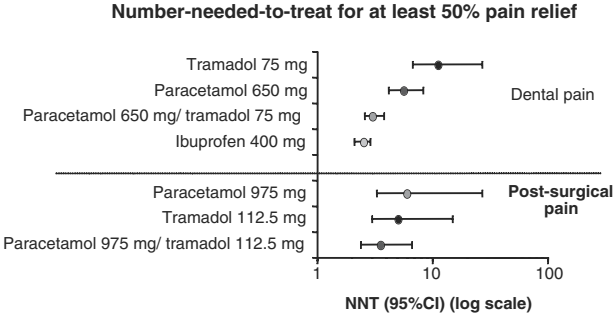

Fig. 2 NNTs for single-dose paracetamol, tramadol, paracetamol plus tramadol, and ibuprofen in dental pain. Reproduced with permission [25]

650 mg plus tramadol 75 mg were mild to moderate, and all were resolved. The main side effects of single-agent tramadol 75 mg or paracetamol 650 mg plus tramadol 75 mg were nausea, dizziness and vomiting.

Efficacy and safety in sub-acute pain

In a study of sub-acute low back pain, the lower dose of tramadol in the paracetamol 325 mg plus tramadol 37.5 mg combination achieved comparable analgesic efficacy and patient satisfaction to tramadol 50 mg alone [26]. Both treatments were well-tolerated, and there were no serious adverse events reported in either treatment group. However, paracetamol plus tramadol showed a significantly reduced incidence of adverse events compared with tramadol alone (50.85% vs 73.33%, respectively; $p<0.01$). There was a significant reduction in adverse events that are normally linked to tramadol, including nausea, vertigo, vomiting and constipation ($p<0.01$–0.05) [26].

Paracetamol plus tramadol has also been studied as an add-on to maintenance NSAID therapy in osteoarthritis flare pain. Here, adding paracetamol plus tramadol to chronic NSAID therapy significantly reduced daily pain intensity over 5 or 10 days compared with NSAID plus placebo ($p<0.001$) (Fig. 3) [27]. There was also a significant improvement in osteoarthritis symptoms compared with placebo according to the Western Ontario and McMaster (WOMAC) questionnaire in three out of the four categories: pain ($p=0.004$ vs placebo), physical function ($p=0.013$ vs placebo) and overall ($p=0.008$ vs placebo). There was no significant difference in joint stiffness between active treatment and placebo ($p=0.100$) [27].

Paracetamol plus tramadol in the management of chronic pain

Chronic pain represents a major challenge for pain management, particularly following regulatory advice to restrict the use of NSAIDs in the long term [28, 29]. A number of studies have investigated the efficacy and safety of paracetamol plus tramadol in the management of different types of chronic pain, either as an alternative to NSAIDs or as an alternative to increasing the dose of existing NSAID therapy.

In a study of more than 300 patients with chronic moderate or severe arthritis pain, patients treated with paracetamol plus tramadol when added to either celecoxib or rofecoxib therapy for 3 months had a significantly lower final mean visual analogue scale (VAS) score and higher pain relief rating scores ($p=0.025$ and $p=0.002$, respectively) compared with patients treated with placebo [30]. This reduced pain was associated with reduced withdrawals. The proportion of patients discontinuing treatment due to lack of efficacy was twice as large in the placebo group (26/17%) compared with the paracetamol plus tramadol group (13/8.5%; $p=0.029$), and the cumulative distribution of time to discontinuation was significantly earlier for placebo ($p=0.016$) (Fig. 4) [30].

Two studies in North America and Canada have tested the efficacy and safety of long-term paracetamol plus tramadol therapy for patients with chronic low back pain [22, 31]. Compared with placebo, this combination significantly reduced pain according to VAS scores during 3 months in both individual study reports and a pooled analysis of both studies ($n=654$) [32]. Final VAS scores in the pooled analysis were 45.9 on paracetamol plus tramadol compared with 57.8 on placebo ($p<0.001$). Almost twice as many patients reported a 50% reduction in VAS score in the treatment group compared with placebo (40.2% vs 23.9%; $p<0.001$). Most importantly, there was also a significant difference in the proportion of patients who experienced a meaningful level of pain relief, which could enable them to begin physiotherapy and rehabilitation. Another clinically important outcome in these studies was quality of life: both individual and pooled study results significantly showed that patients were not as bothered anymore ($p<0.001$ overall) and total scores ($p=0.002$ overall) in the Roland Disability Questionnaire [22, 31, 33] also improved significantly. Similarly, the physical and mental component summary outcomes on the short-form-36 (SF-36) questionnaire were significantly better on

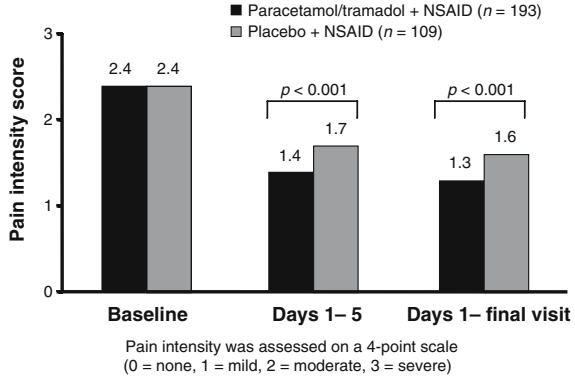

Fig. 3 Comparison of combination vs placebo against osteoarthritis flare pain. Reproduced with permission [27]

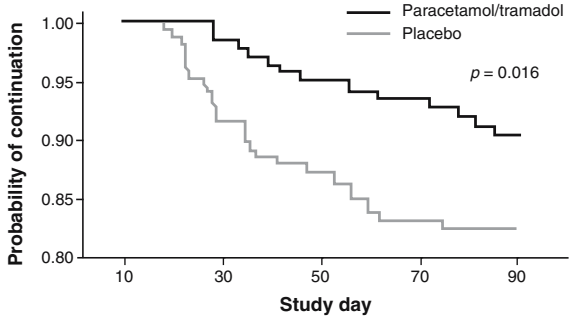

Fig. 4 Probability of patients continuing therapy (measures rate of discontinuation from the study due to lack of efficacy) with paracetamol plus tramadol vs placebo as add-on therapy to a COX-2 selective NSAID. Based on trial data reported by Emkey [30] (Grünenthal, data on file)

paracetamol plus tramadol than placebo (p=0.008 and p=0.015, respectively) in the pooled analysis [33].

Paracetamol plus codeine is the most widely used combination of paracetamol with a weak opioid agent. A comparison of paracetamol 325 mg plus tramadol 37.5 mg vs paracetamol 300 mg plus codeine 30 mg demonstrated similar analgesic efficacy in the management of chronic low back pain and/or osteoarthritis pain during 4 weeks of therapy [34]. Although the overall incidence of adverse events was comparable in both treatment groups (71% on paracetamol plus tramadol vs 76% on paracetamol plus codeine), both somnolence and constipation were reduced on the tramadol combination compared with paracetamol plus codeine (17% vs 24%; p<0.05 and 11% vs 21%; p<0.01, respectively) [34]. A 23-month open-label extension of this study confirmed that the analgesic efficacy of paracetamol plus tramadol was sustained (Fig. 5) [23]. There was no evidence of any development of tolerance: maximum pain relief remained between 2.2 and 2.7 using the Likert scale (0=none; 1=little; 2=some; 3=a lot; 4=complete) throughout 2 years of treatment. The results were also consistent with a lack of tolerance; the average daily dose was between 4.9 and 5.2 tablets from week 13 until the end of the study [23]. The average daily and average maximum daily doses were much lower than the maximum daily doses for each medication at paracetamol/tramadol 1,363/157 mg and 2,178/251 mg, respectively. Long-term adverse events were similar to those observed during the 4-week controlled study [23].

Fibromyalgia is a complex condition that may be viewed as the result of a central sensitisation process because it involves abnormal sensory processing and is refractory to treatment with NSAIDs [35–38]. The multi-modal actions of paracetamol and tramadol and possibly the specific effect of tramadol on neuropathic pain [39] make this combination a rational choice for pain in fibromyalgia; this hypothesis has been tested in a 3-month placebo-controlled trial [40]. Paracetamol plus tramadol significantly improved VAS score compared with placebo (53 vs 65; p<0.001), and it also had lower cumulative rates of discontinuation both due to lack of efficacy and side effects than placebo (29% vs 51%; p<0.001 and 48% vs 62%; p=0.004). Whilst this should not be misread as a curative approach to fibromyalgia, it might enable patients to return to more normal activities and participate in the aerobic conditioning essential to their improvement [41]. Fibromyalgia symptoms were reduced as measured using the Fibromyalgia Impact Questionnaire (FIQ; total score 44 on study drug vs 50 on placebo; p=0.008). Almost all FIQ subscales were significantly improved by paracetamol plus tramadol, including physical impairment, "feel good", "do job" and pain (p=0.02, p=0.001, p=0.04, p=0.02 vs placebo, respectively) [40]. Health-related quality of life according to SF-36 showed a similar effect for the study drug, with significant improvements in physical functioning (p=0.005), role-physical (p=0.001) and bodily pain (p=0.002) compared with placebo [40, 42]. These results suggest that paracetamol plus tramadol produced a clinically important benefit that could help patients return to normal activities.

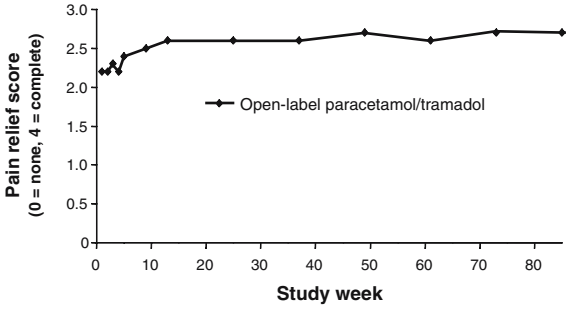

Fig. 5 Long-term efficacy of paracetamol plus tramadol in osteoarthritis and low-back pain (Grünenthal, data on file)

Conclusions

Rationally designed multimodal combination therapy for pain offers the potential to improve efficacy and/or tolerability and safety compared with single-agent analgesia. Paracetamol plus tramadol is a rational combination that utilises the complementary pharmacodynamics (different mechanisms of action) and pharmacokinetics (different onset and duration of action) of the two agents.

This combination has shown good efficacy in the control of acute post-operative pain and sub-acute pain due to osteoarthritis flare or low back injury. In the context of current safety concerns about long-term use of anti-inflammatory drugs, it is important to note that paracetamol plus tramadol has also demonstrated efficacy in the control of a variety of chronic pain states with associated functional improvement. Such data are available for use in osteoarthritis, chronic low back pain and fibromyalgia, even for long-term treatment up to 2 years' duration.

Paracetamol plus tramadol is well-tolerated and has shown in studies a marked reduction in adverse events compared with equianalgesic doses of tramadol alone or other combination preparations.

Hence, paracetamol plus tramadol offers an effective alternative to COX-2 selective or non-selective NSAIDs, which is also safe as it lacks their organ toxicity. Even in patients who remain on long-term NSAID treatment, paracetamol plus tramadol is a useful add-on analgesic treatment if existing therapy is insufficiently effective, for example during osteoarthritis flares.

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