

Trial of tramadol/acetaminophen tablets for osteoarthritis pain in subjects receiving a COX-2 nonsteroidal antiinflammatory drug.

Michael H Ellman and James Curran

J Rheumatol 2005;32;568

<http://www.jrheum.org/content/32/3/568.citation>

1. Sign up for TOCs and other alerts
<http://www.jrheum.org/alerts>
2. Information on Subscriptions
<http://jrheum.com/faq>
3. Information on permissions/orders of reprints
http://jrheum.com/reprints_permissions

The Journal of Rheumatology is a monthly international serial edited by Earl D. Silverman featuring research articles on clinical subjects from scientists working in rheumatology and related fields.

Correspondence

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited; however, it should not exceed 800 words, with a maximum of 10 references and no more than 2 figures (submitted as camera ready hard copy per Journal Guidelines) or tables and no subdivision for an Abstract, Methods, or Results. Letters should have no more than 4 authors. Full name(s) and address of the author(s) should accompany the letter as well as the telephone number, fax number, or E-mail address.

Contact. The Managing Editor, The Journal of Rheumatology, 365 Bloor Street East, Suite 901, Toronto, ON CANADA M4W 3L4. Tel: 416-967-5155; Fax: 416-967-7556; E-mail: jrheum@jrheum.com Financial associations or other possible conflicts of interest should always be disclosed.

Trial of Tramadol/Acetaminophen Tablets for Osteoarthritis Pain in Subjects Receiving a COX-2 Nonsteroidal Antiinflammatory Drug

To the Editor:

Emkey, *et al*¹ describe the effectiveness and safety of tramadol combined with acetaminophen as treatment for symptomatic osteoarthritis (OA) of the knee or hip in patients already receiving a cyclooxygenase-2 (COX-2) selective drug. The study conclusions have deficiencies, in our opinion, that we believe warrant comment. Having a drug combination of 2 analgesics, tramadol and acetaminophen, as the treatment arm makes it very difficult to sort out which one of the 2 was beneficial. This is gently commented on in an accompanying editorial². We understand that the study was supported by the manufacturer of the drug combination, but a third arm with either acetaminophen or tramadol alone would help focus on which drug was contributing the most to the analgesia and the side effects. We were also concerned about the short duration of the study in patients with chronic joint pain. Three months, the duration of this study, is not a very long time for patients with chronic pain.

We were especially concerned about adverse events and we conclude that the addition of tramadol/acetaminophen combination to a COX-2 drug might not be safe. After all, in Table 3, fully 18 out of 153 patients receiving the drug combination had somnolence, 23 had nausea, 20 complained of constipation, 10 had fatigue, 4 experienced vomiting, and 10 had dizziness. These reported adverse events were much less common in the placebo group. We understand that some of these reported events might be very mild and several may be occurring in the same patients. The average age of the study patients was only 61 years and it is likely that in an older population of patients with OA, side effects such as somnolence, for instance, might occur even more frequently and be more severe. Our patients with chronic OA are generally older than 61 years.

Neither the authors¹ nor Dr. Altman² mention the cost of this drug

combination. The mean tramadol/acetaminophen use was 4.1 tablets in the study. At our university pharmacy, 100 Ultracet[®] tablets retail for \$115, or more than \$4 a day for the average patient in this study. Of course this is in addition to the COX-2 drug.

We don't mean to be critical about this helpful study that was performed well. A trial of tramadol with acetaminophen might be helpful in OA pain, but side effects and cost are important issues that need to be discussed more fully, and longer term use of this drug combination is needed to verify efficacy.

MICHAEL H. ELLMAN, MD; JAMES CURRAN, MD, The Department of Medicine, Section of Rheumatology, University of Chicago, 5841 South Maryland Avenue (MC 0930), Chicago, Illinois 60637, USA. E-mail: mellman@medicine.bsd.uchicago.edu

REFERENCES

1. Emkey R, Rosenthal N, Wu S-C, Jordan D, Kamin M, for the CAPSS-114 Study Group. Efficacy and safety of tramadol/acetaminophen tablets (Ultracet[®]) as add-on therapy for osteoarthritis pain in subjects receiving a COX-2 nonsteroidal antiinflammatory drug: A multicenter randomized, double-blind, placebo-controlled trial. *J Rheumatol* 2004;31:150-6.
2. Altman RD. Pain relief in osteoarthritis: The rationale for combination therapy [editorial]. *J Rheumatol* 2004;31:5-7.

Dr. Emkey replies

To the Editor:

The authors thank Drs. Ellman and Curran for their comments on our study of tramadol/acetaminophen (APAP) as add-on therapy for patients with osteoarthritis (OA) receiving concomitant therapy with cyclooxygenase-2 (COX-2) selective nonsteroidal antiinflammatory drugs (NSAID; celecoxib or rofecoxib). They raise some important issues to which we would like to respond.

Factorial design studies have already described the analgesic superiority of tramadol/APAP combination tablets over each of the components¹⁻³. Tramadol/APAP tablets also have demonstrated superior efficacy and a lower incidence of adverse effects than high-dose tramadol tablets⁴. Comparisons of tramadol/APAP tablets with other opioid combinations such as high-dose hydrocodone/APAP⁵ and codeine/APAP^{6,7} have shown comparable efficacy but significantly lower rates of typical opioid adverse effects such as nausea, vomiting, or constipation.

In our add-on study of safety and efficacy, 153 patients taking a mean daily dose of 4.1 tablets (154 mg tramadol/1332 mg APAP) in combination with a COX-2 selective NSAID experienced typical opioid adverse events such as nausea (15%), constipation (13%), and somnolence (12%). The generally mild to moderate intensity of these events is illustrated in the cumulative total of treatment-limiting adverse effects. In total, only 13% of tramadol/APAP patients discontinued therapy due to adverse events. In contrast, in the largest trials of tramadol for OA, 39% of tramadol patients discontinued due to treatment-limiting adverse events^{8,9}. In one of these trials, 146 continuing patients took an average tramadol dose of 256 mg/day over the last 2 weeks of a 39-day trial⁹. The lower rate of discontinuation due to adverse events found with tramadol/APAP in our study may be explained in part by the lower average daily dose of tramadol as a result of the tramadol-sparing role of APAP.

Although our study sample was not large enough to separate a sufficiently powered elderly subset, such analyses have been done in other studies of tramadol/APAP for OA flare¹⁰ and 3-month trials for low back pain¹¹. Both studies found that the elderly tolerability profile was similar to that experienced in the overall study populations. Caution, however, about

generalizing these results to frail elderly patients with complex medical conditions is warranted since our studies were conducted in relatively healthy individuals.

With respect to the cost of therapy, data on healthcare resource utilization were not collected in this study, so a full economic evaluation of overall healthcare cost could not be undertaken. The potential economic benefit of tramadol/APAP combination tablets is suggested by the reduced rate of adverse events as well as rates of discontinuation compared with other opioid medications¹², both of which may lead to lower healthcare cost and utilization. Further studies are needed to examine this question.

RONALD EMKEY, MD, Radiant Research/Reading, 1235 Penn Avenue, Suite 200, Wyomissing, Pennsylvania 19610, USA.
E-mail: ronaldemkey@radiantresearch.com

REFERENCES

1. Medve RA, Wang J, Karim R. Tramadol and acetaminophen tablets for dental pain. *Anesth Prog* 2001;48:79-81.
2. Edwards JE, McQuay HJ, Moore RA. Combination analgesic efficacy: individual patient data meta-analysis of single-dose oral tramadol plus acetaminophen in acute postoperative pain. *J Pain Symptom Manage* 2002;23:121-30.
3. McQuay H, Edwards J. Meta-analysis of single dose oral tramadol plus acetaminophen in acute postoperative pain. *Eur J Anaesthesiol* 2003;20 Suppl 28:19-22.
4. Fricke JR Jr, Hewitt DJ, Jordan DM, Fisher A, Rosenthal NR. A double-blind placebo-controlled comparison of tramadol-acetaminophen and tramadol in patients with postoperative dental pain. *Pain* 2004;109:250-7.
5. Fricke JR Jr, Karim R, Jordan D, Rosenthal N. A double-blind, single-dose comparison of the analgesic efficacy of tramadol/acetaminophen combination tablets, hydrocodone/acetaminophen combination tablets, and placebo after oral surgery. *Clin Ther* 2002;24:953-68.
6. Mullican WS, Lacy JR. Tramadol/acetaminophen combination tablets and codeine/acetaminophen combination capsules for the treatment of pain: a comparative trial. *Clin Ther* 2001;23:1429-45.
7. Smith AB, Ravikumar TS, Kamin M, Jordan D, Xiang J, Rosenthal N. Combination tramadol plus acetaminophen for postsurgical pain. *Am J Surg* 2004;187:521-7.
8. Adler L, McDonald C, O'Brien C, Wilson M. A comparison of once-daily tramadol with normal release tramadol in the treatment of pain in osteoarthritis. *J Rheumatol* 2002;29:2196-9.
9. Dalgin P, TPS-OA Study Group. Comparison of tramadol and ibuprofen for the chronic pain of osteoarthritis [abstract]. *Arthritis Rheum* 1997;40 Suppl:S86.
10. Rosenthal NR, Silverfield JC, Wu SC, Jordan D, Kamin M. Tramadol/acetaminophen combination tablets for the treatment of pain associated with osteoarthritis flare in an elderly patient population. *J Am Geriatr Soc* 2004;52:374-80.
11. Peloso P, Rosenthal N, Wu S, Jordan D. A pooled analysis of tramadol/acetaminophen tablets for treatment of lower back pain in an elderly patient population [abstract]. *J Am Geriatr Soc* 2003;51 Suppl 4:S143-4.
12. Peloso PM, Bellamy N, Bensen W, et al. Double blind randomized placebo control trial of controlled release codeine in the treatment of osteoarthritis of the hip or knee. *J Rheumatol* 2000;27:764-71.

Book Review

Low Back and Neck Pain: Comprehensive Diagnosis and Management, Third Edition. David G. Borenstein, Sam W. Wiesel, and Scott D. Boden. Philadelphia; Saunders, 2004, 729 pages, price: \$99.00 US

As the title implies, this 729-page textbook aims to provide a comprehensive description of the medical approach to back and neck pain. Its 20 chapters organized in 4 sections cover from basic anatomy and biomechanics to nosology, clinical evaluation, and therapy.

On the plus side, the text is indeed comprehensive and authoritative, often providing clear direction and recommendations for assessment and management. It also shows awareness of recent research and the impact of psychosocial factors on the prognosis and response to treatment. The initial chapters on anatomy and biomechanics are concise and provide necessary background to grasp the complexities of neck and back pain. The chapters on alternative and complementary therapies are a welcome addition.

On the minus side, the authoritative approach to the text gives the impression that we know more than we really do. It provides little discussion of concepts that challenge the traditional biomedical view of causation, such as referral pain patterns from somatic structures, central sensitization in chronic pain, and the theories of pain of muscle origin. A great part of the text (380 pages) is devoted to conditions seldom seen in primary or secondary medical practice such as tumors and rheumatic and endocrinology conditions. In some chapters the authors' recommendations seem somewhat unrelated to their assessment of evidence from trials, but to the authors' credit, the recommendations and trial sections are clearly marked.

Overall, this is a useful reference textbook that will make a worthwhile addition to the libraries of practitioners caring for people with back and neck pain. It provides a comprehensive review of the multiple conditions that can produce these symptoms. Compared with textbooks on similar topics published by Alf Nachemson and Gordon Waddell this text provides more clinical advice, but perhaps less strict grounding on available scientific evidence.

JAIME GUZMAN, MD, MSc, FRCPC, Assistant Professor of Medicine, University of Toronto, Associated Scientist, Institute for Work & Health, Clinician Investigator, Toronto Rehabilitation Institute, Toronto, ON, Canada.

Correction

Atkinson JH. Chronic back pain: searching for causes and cures. *J Rheumatol* 2004;31:2323-5. On page 2325, in the closing paragraph of the text, reference "18" should correctly be reference 17. We regret the error.