Letter to the Editor

Dear Dr Dummer

I read with great interest the recent article by Mellor *et al.* evaluating five patients who received intra-oral injection of ketorolac and five who received placebo (Mellor *et al.* 2005). Their finding of limited analgesic efficacy of peripherally administered ketorolac is interesting as the analgesic efficacy following local/topical administration of ketorolac has been demonstrated in several double blind placebo controlled clinical trials evaluating patients after endodontic (Penniston & Hargreaves 1996; Rogers *et al.* 1999), ophthalmic (Brint *et al.* 1999; Heier *et al.* 1999) or orthopedic (Calmet *et al.* 2002) procedures. It is possible that this lack of detected effect is because of the limited sample size of the study, the pain scale employed, or the time course evaluated. At least some expert panels (Caraceni *et al.* 2002) have concluded that the McGill pain scale may have low sensitivity for detecting treatment interventions compared with other pain scales such as the visual analog scale (VAS). Although the VAS was used in the Mellor *et al.* study, the actual time response effects were not reported and therefore it is difficult to interpret the findings. Instead, only baseline data was provided. For example, in our study, peak analgesic effects occurred 30 min after injection and, accordingly, it would be important to know how long the patients were followed in the Mellor *et al.* study.

We also reported a transient pain sensation following intraoral injection of ketorolac, but none of the 18 patients injected with intraoral ketorolac withdrew from the study (Penniston & Hargreaves 1996). This latter point should be appreciated: none of the intraoral ketorolac patients elected to withdraw from our study and receive rescue medication. A similar report of transient pain is found in clinical trials evaluating local/topical administration of ketorolac in patients after ophthalmic procedures (Aragona *et al.* 2000). Interestingly, direct application of ketorolac onto peripheral or central nerves appears to be well tolerated in humans and rats (Reinhart *et al.* 2000; Korkmaz *et al.* 2004), and therefore a direct neurotoxic mechanism does not appear to mediate this effect. The actual mechanism remains unknown, but does not appear to be associated with gross cytotoxic effects as epithelial damage is not observed after repeated ketorolac application to normal human cornea (Aragona *et al.* 2000) and wound healing appears normal following repeated local application of ketorolac after opthalmic surgical procedures (Heier *et al.* 1999).

It is difficult to evaluate the actual adverse effect size (i.e., VAS scores) in the Mellor *et al.*, study. Although the abstract and discussion stated five times that ketorolac produced 'significant' pain or discomfort, neither the VAS magnitude nor an actual statistical analysis was provided. Thus, the basis for five statements of 'significant' pain is unknown. The commentary from Professor Newcombe is interesting because of the conclusion that ketorolac is a 'harmful intervention' that represents an 'inferior treatment' completely ignores larger clinical trials evaluating this same compound in endodontic patients where all treated patients continued to participate in the trial and the intervention produced significantly greater analgesia compared to placebo. It is difficult to understand evidence-based recommendations that are not based on all of the published evidence.

Injectable ketorolac has been evaluated in multiple clinical trials and is the subject of a systematic review (http://www.jr2.ox.ac.uk/bandolier/booth/painpag/Acutrev/Analgesics/AP023.html). The Mellor *et al.*, study represents a potentially important contribution to this body of work by confirming our report of an adverse effect upon introral injection. However, as the authors make clinical recommendations based upon a small sample size, claim five times that the effect is significant, but without reporting the magnitude of the adverse effect or the statistical analysis, caution is advised in interpreting this study.

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References

Aragona P, Tripodi G, Spinella R, Lagana E, Ferreri G (2000). The effects of the topical administration of non-steroidal anti-inflammatory drugs on corneal epithelium and corneal sensitivity in normal subjects. *Eye* **14** (Pt 2), 206–10.

Brint SF, Cheetham J, Degryse R, Abel M, Thompson V, Rosenthal A (1999). Efficacy and safety of nonpreserved ketorolac ophthalmic solution in postoperative ocular pain following radial keratotomy. *Journal of Cataract and Refractive Surgery* **25**, 41–9.

Calmet J, Esteve C, Boada S, Gine J (2002). Analgesic effect of intra-articular ketorolac in knee arthroscopy: comparison of morphine and bupivacaine. *Knee Surgery, Sports Traumatology, Arthroscopy* **12**, 552–5.

Caraceni A, Cherny N, Fainsinger R et al. (2002). Pain measurement tools and methods in clinical research in palliative care: recommendations of an Expert Working Group of the European Association of Palliative Care. *Journal of Pain and Symptom Management* **23**, 239–55.

Heier J, Cheetham J, Degryse R et al. (1999). Ketorolac tromethamine 0.5% ophthalmic solution in the treatment of moderate to severe ocular inflammation after cataract surgery: a randomized, vehicle-controlled clinical trial. *American Journal of Ophthalmology* **127**, 253–9.

Korkmaz HA, Maltepe F, Erbayraktar S et al. (2004). Antinociceptive and neurotoxicologic screening of chronic intrathecal administration of ketorolac tromethamine in the rat. *Anesthesia and Analgesia* **98**, 148–52.

Mellor AC, Dorman ML, Girdler NM (2005). The use of an intra-oral injection of ketorolac in the treatment of irreversible pulpitis. *International Endodontic Journal* **38**, 789–92.

Penniston S, Hargreaves K (1996). Evaluation of periapical injection of Ketorolac for management of endodontic pain. *Journal of Endodontics* **22**, 55–9.

Reinhart D, Stagg K, Walker K et al. (2000). Postoperative analgesia after peripheral nerve block for podiatric surgery: clinical efficacy and chemical stability of lidocaine alone versus lidocaine plus ketorolac. *Regional Anesthesia and Pain Medicine* **25**, 506–13.

Rogers MJ, Johnson BR, Remeikis NA, Begole EA (1999). Comparison of effect of intracanal use of ketorolac tromethamine and dexamethasone with oral ibuprofen on post treatment endodontic pain. *Journal of Endodontics* **25**, 381–5.

Response from authors

Dear Editor,

We thank Professor Hargreaves for his interest in our paper.

The McGill scale was used in this study to measure pain at baseline before the procedure was started and then again at 6 and 24 h to measure pain relief from the pulpitis. Because we had not anticipated any more than transient pain from the intra-oral injection itself, the patient's pain level was not measured after the injection. We agree that the McGill scale would not have been a useful instrument in this situation.

Professor Hargreaves queries our use of the term 'significant' to describe the pain after the injection of ketorolac. We agree this is a purely subjective judgement by the clinician involved (Dr Mellor) based on 30 years clinical experience. This was not just pain on actual injection, it was pain that continued until local anaesthetic was given in that area for the procedure itself (in the maxilla) or for the duration of the visit (in the mandible). Patients were not kept beyond the extent of the treatment so the length of time that the post-injection pain lasted was not measured. The study was terminated early by Dr Mellor as he felt unhappy at administering a painful injection when the whole point of the study was to make the procedure more painless. In addition, the successful pulp extirpation rate was no different in the small number of patients treated.

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Dear Editor

As a general principle I wholeheartedly agree with any plea to interpret study findings with caution. Nevertheless what was presented in this article is a clear, simple statement by researchers that, having tried their test regime on a small number of patients in blinded RCT conditions, they reached the conclusion that it was ethically unacceptable to continue to offer this treatment, and acted upon it. Probably it's not for me to judge whether that was the 'right' decision for them to make – whatever that means – but that is what happened. Professor Hargreaves points out that in his study with Penniston, no patient undergoing an intraoral Ketorolac injection chose to withdraw. It appears that none of Mellor *et al.*'s patients actually withdrew following Ketorolac injection, either, but four of the first five made it clear that this was very unpleasant.

On reading Hargreaves' remarks, my reaction was to ask, just how far is the statistical reviewer role meant to extend? I don't think the onus should have been on me to find out that the McGill pain scale may have limited sensitivity, still less to systematically review the evidence in favour of Ketorolac in a variety of contexts. I'm all in favour, in principle, of the idea that articles