Dexketoprofen-induced antinociception in animal models of acute pain: Synergy with morphine and paracetamol

H.F. Miranda*, M.M. Puig, C. Dursteler, J.C. Prieto, G. Pinardi

Pharmacology Program, ICBM, Faculty of Medicine, University of Chile, Independencia 1027, Santiago 7, Chile

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E-mail address: hmiranda@ubiobio.cl (H.F. Miranda).

The antinociceptive activity of dexketoprofen was studied in mice using the acetic acid writhing test (acute tonic pain), the tail flick test (acute phasic pain) and the formalin assay (inflammatory pain). Isobolographic analysis was used to study the antinociceptive interactions between morphine and paracetamol co-administered with dexketoprofen. In the writhing test, the intraperitoneal administration of dexketoprofen or ketoprofen resulted in parallel dose—response curves with equal efficacy, but higher relative potency for dexketoprofen. In the tail flick test, the curves were parallel with similar efficacy and potency. The administration of morphine or paracetamol in both tests resulted in dose—response curves not parallel with that of dexketoprofen, which showed a potency between morphine and paracetamol. In the formalin assay, the antinociceptive activity of morphine during phase I was 122, 295 and 1695 times higher than dexketoprofen, ketoprofen and paracetamol, respectively. Isobolographic analysis demonstrated that the combination of sub-analgesic doses of dexketoprofen with morphine or with paracetamol was strongly synergic in all three tests. Synergistic drug combinations should improve effective pharmacological treatment of pain, minimizing drug specific adverse effects. These findings are undoubtedly worthy of additional controlled clinical trials in severe pain syndromes.

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Dose—response in direct comparisons of different doses of aspirin, ibuprofen and paracetamol (acetaminophen) in analgesic studies

H.J. McQuay*, R.A. Moore

Pain Research and Nuffield Department of Anaesthetics, University of Oxford, Churchill Hospital, Headington, Oxford OX3 7LJ, United Kingdom

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E-mail address: henry.mcquay@pru.ox.ac.uk (H.J. McQuay).

Aims: Establishing the dose—response relationship for clinically useful doses of aspirin, ibuprofen and paracetamol has been difficult. Indirect comparison from meta-analysis is compromised by too little information at some doses.

Methods: A systematic review of randomized, double-blind trials in acute pain comparing different doses of aspirin, ibuprofen and paracetamol was therefore undertaken.

Results: Fifty trials were found. Numerical superiority of higher over lower dose was found by the original authors in 37/50 trials (74%) and statistical superiority in 11/50 (22%). Twenty-eight trials had design, quality and data reporting characteristics to allow pooling of common doses; in 3/28 (11%) of the individual trials our calculations showed statistical superiority of higher over lower dose. Pooled comparison of 1000/1200 mg aspirin over 500/600 mg was statistically superior, with a number-needed-to-treat (NNT) for higher over lower dose of 16 (8 to >100). Pooled comparison of 400 mg ibuprofen over 200 mg was statistically superior, with an NNT for higher over lower dose of 10 (6—23). Pooled comparison of 1000 mg paracetamol over 500 mg was statistically superior, with an NNT for higher over lower dose of 9 (6—20).

Conclusions: Use of trials making direct comparison of two different doses of target drugs revealed the underlying dose—response curve for clinical analgesia.

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