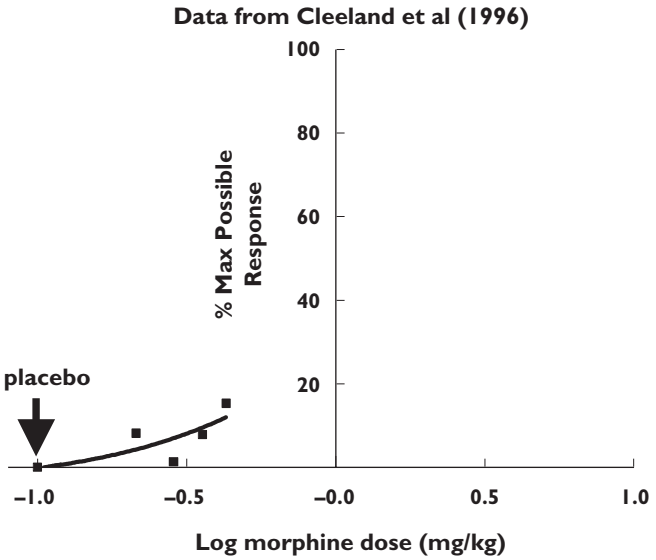

Figure 1
Cold pressure Test Tolerance response data expressed as percentage of the maximum possible response (■) show 0.25 mg kg^{-1} of morphine corresponds to the ED_{10}

et al. unpublished data). These findings suggest that morphine:oxycodone combinations produce greater than additive (and likely synergistic) pain relief in patients.

In summary, extrapolation of findings from an antinociception study in healthy subjects using single doses of opioids either individually or in combination, without prior adequate identification of the pharmacodynamic range for the pain being tested, needs reassessment. In order to be of predictive value, studies of antinociceptive synergy in healthy subjects need to be carefully designed, taking into consideration the full pharmacological range of the drugs being studied.

References

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Author's response

Response to Smith MT and de la Iglesia FA: 'Coadministration of oxycodone and morphine and analgesic synergy re-examined.'

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We thank Drs Smith and de la Iglesia for their thoughtful comments and for providing the important information generated by transforming the cold pressor test tolerance data regarding the efficacy of different morphine doses [1] into a percentage of the maximum possible response.

Several aspects of Smith and de la Iglesia's approach deserve special attention. First, a significant discrepancy between animals and humans regarding the dosage needed to produce a morphine/oxycodone synergistic effect emerges from the data presented in their letter. While the doses used in the rats [2] were subantinociceptive (producing levels of antinociception similar to those produced by saline), in the human study [3] the mean daily rescue dose of morphine and the mean constant dose of oxycodone were clearly within the clinical antinociceptive range. Second, we are not aware of any published data regarding the ED_{50} doses of oxycodone and morphine, either alone or in combination, required for reducing cancer pain. Yet, according to Lauretti *et al.* [3], a synergistic effect between the two drugs was apparent during the first week of oxycodone treatment, when the mean morphine/oxycodone doses were l0 mg and 40 mg, respectively, as well as during the last week of oxycodone treatment, when the respective morphine/oxycodone doses were 10 mg and 70 mg. Until pub-

lished, one can only wonder what opioid dosages were administered in the osteoarthritis studies and upon what basis. Thus, in contrast to Smith and de la Iglesia's view, it seems that the morphine/oxycodone synergy in humans may not necessarily require precise dosing. Third, it is true that we did not conduct preliminary dose-response experiments. We therefore used dosages that were based on published literature [1], as well as on what seemed to us like a clinically relevant range of doses. Fourth, we wish to emphasize the clear conclusion of our study [4], according to which the results refer only to the tested doses of opioids and to the specific experimental conditions used in the study. We purposefully avoided extrapolating these findings to any clinical conditions. Fifth, the currently available clinical trials may suggest a possible synergistic effect of the two drugs in cancer patients and perhaps in osteoarthritic patients. A naive reader may misinterpret Smith and de la Inglesia's suggestion that 'morphine: oxycodone combinations produce greater than additive (and likely synergistic) pain relief in patients' by generalizing such a conclusion to additional pain populations that have never actually been studied in this context. May we therefore suggest that this conclusion be modified accordingly. Lastly, we disagree in part with Smith and de la Inglesia's statement regarding the questionable suitability of the cold pressor test 'to predict clinical relevant doses of opioids.' It is true that all tested doses in our study produced only a minimal effect on the magnitude of pain evoked by the cold stimulation. However, the clinically relevant dose of 0.5 mg kg^{-1} of oral morphine increased the latency to pain onset by 47% compared to baseline, and the maximal increase produced by an equal dose of oxycodone was 120%. These magnitudes of effect are by all means large enough for the study of clinical conditions such as thermal hyperalgesia.

References

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