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Letter to the Editors

Co-administration of oxycodone and morphine and analgesic synergy re-examined

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The paper by Grach *et al.* [1] in the Journal addresses the little explored potential benefit of combination opioids in analgesia. Compared with a published study documenting oxycodone-morphine synergy in rats [2], the antinociception study by Grach *et al.* in healthy subjects has significant design limitations to support their conclusions.

In rats, antinociception dose–response curves were produced for each of oxycodone and morphine for the relief of noxious thermal pain [2]. Baseline responses increased 3-fold and antinociceptive ED_{50} doses of oxycodone and morphine were 2.8 and 8.5 mg kg^{-1}, respectively. These ED_{50} values agreed with previously published data [3]. Dose–response curves employing oxycodone:morphine combination at ratios of 3 : 1, 1 : 1 and 1 : 3 relative to the morphine or oxycodone ED_{50} alone, were constructed. Marked antinociceptive synergy was demonstrated using isobolographic analysis and validated by using selective antagonists for each of the combination components.

In their study, Grach *et al.* compared oral doses of 0.5 mg kg^{-1} morphine or 0.5 mg kg^{-1} oxycodone with 0.25 mg kg^{-1} morphine combined with 0.25 mg kg^{-1} oxycodone. The morphine dose selected was the lowest dose (0.43 mg kg^{-1}) identified by Cleeland *et al.* [4] that produced significant antinociception in the cold pressor test. We have re-calculated the cold pressor tolerance (CPT) data as a percentage of the maximum possible response (see Figure 1).

According to the Cleeland study [4], only the largest dose of oral morphine tested (0.43 mg kg^{-1}) produced significant antinociception compared with the active diphenhydramine placebo. Thus the assumptions were that the Median Baseline response was 30 s and the Minimum acceptable dynamic range was three times the baseline response, similar to the rodent antinociception criteria. The Percentage Maximum Possible Effect (%MPE) was calculated as the percentage difference between the measured response and the baseline response, divided by the difference between the maximum response and the baseline response.

Figure 1 shows that 0.25 mg kg^{-1} morphine approximates the ED_{10}. Using the same approach as Grach *et al.* (0.25 mg kg^{-1} morphine and oxycodone) represents, at best, the ED_{10} and ED_{25}, respectively. Without additional dose–response data, it is not possible to confidently identify the effective doses of the individual opioids, the subantinociceptive dose range for cold pressor pain, or the doses needed to produce an adequate pharmacodynamic range in healthy subjects. Furthermore, their study highlights the poor sensitivity of this test for predicting clinically relevant doses of opioids as seen with morphine [4]. Thus, an alternative conclusion of this work is that the suitability of the cold pressor test to predict clinically relevant doses of opioids, administered alone or in combination, is questionable under the conditions of this study.

Laurettti *et al.* in 2003 [5] reported opioid synergy in chronic cancer-related pain. Briefly, 22 patients received controlled-release morphine (CRM) and controlled-release oxycodone (CRO) in a crossover design involving two sequential 14-day treatment periods with immediate-release morphine (IRM) available for breakthrough pain. The requirement for breakthrough IRM was 38% higher in patients receiving CRM than in patients receiving CRO, suggesting that a synergistic analgesic interaction took place when morphine was administered to patients receiving CRO.

In two double-blind, crossover studies involving 44 osteoarthritic patients with moderate to severe pain, the steady-state daily opioid requirements were approximately 40% less with morphine:oxycodone combinations compared with morphine alone (Smith

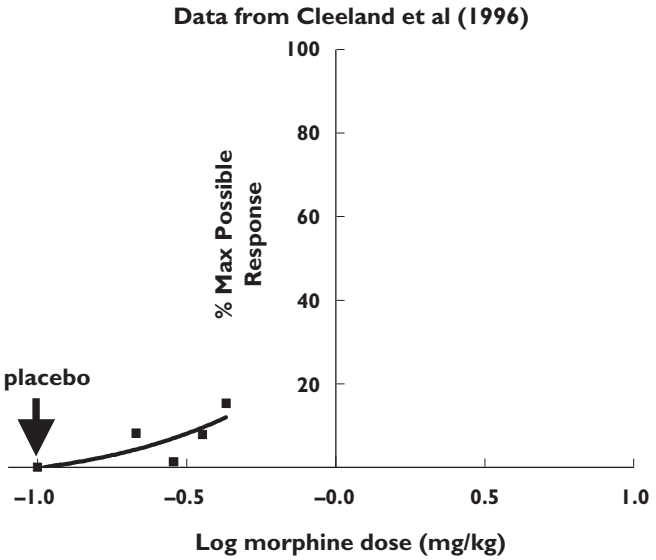

Figure 1
Cold pressure Test Tolerance response data expressed as percentage of the maximum possible response (■) show 0.25 mg kg^{-1} of morphine corresponds to the ED_{10}

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.

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1 Cleeland CS, Nakamura Y, Howland EW, Morgan NR, Edwards KR, Backonja M. Effects of morphine on cold pressor tolerance time and neuropsychological performance. Neuropsychopharmacology 1996; 15: 252–62.

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