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Gabapentin enhances the analgesic effect of morphine in healthy volunteers.

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Abstract

The most effective group of drugs for the treatment of severe pain is opioid analgesics. Their use, however, is limited by decreased effects in neuropathic and chronic pain as a result of increased pain and development of tolerance. Gabapentin (GBP) is effective in both experimental models of chronic pain and clinical studies of neuropathic pain. Therefore, we investigated, in a randomized, placebo-controlled, double-blinded study, the pharmacodynamic and pharmacokinetic interaction of GBP and morphine in 12 healthy male volunteers. Morphine (60 mg, controlled release) or placebo was administered at 8:00 AM, and GBP (600 mg) or placebo was administered at 10:00 AM, thus comparing the analgesic effect of placebo + GBP (600 mg) with placebo + placebo and morphine (60 mg) + GBP in comparison to morphine plus placebo by using the cold pressor test. The duration and intensity of the side effects were assessed by using visual analog scales. The analgesic effect was evaluated by the change in the area under the curve (h x %; 0% baseline before Medication 1) of pain tolerance. Placebo + GBP (18.9% x h, 95% confidence interval [CI]: -2.5 to 40.3) did not present any significant analgesic effect compared with placebo + placebo (4.7% x h, 95% CI: -16.7 to 26.1). A significant increase in pain tolerance was observed comparing the combination of morphine and GBP (75.5% x h, 95% CI: 54.0-96.9) with morphine + placebo (40.6% x h, 95% CI: 19.2-62.0). The observed adverse events after placebo + GBP were not significantly different compared with placebo + placebo. Morphine + placebo led to the expected opioid-mediated side effects. They were significantly more pronounced compared with placebo + placebo but did not differ significantly compared with the combination of morphine + GBP. Concerning the pharmacokinetic variables of morphine and its glucuronides, no significant difference between morphine + placebo and morphine + GBP was observed, whereas the area under the curve of GBP (43.9 +/- 5.3 vs 63.4 +/- 16.2 microg. h(-1). mL(-1), $P < 0.05$) significantly increased, and apparent oral clearance (230.8 +/- 29.4 mL/min vs 178 +/- 97.9 mL/min, $P = 0.06$) and apparent renal clearance (86.9 +/- 20.6 vs 73.0 +/- 24.2 mL/min, $P = 0.067$) of GBP decreased when morphine was administered concomitantly. These results suggest two different sites for the pharmacokinetic interaction-one at the level of absorption and the other at the level of elimination. Our study reveals both a pharmacodynamic and pharmacokinetic interaction between morphine and GBP, leading to an increased analgesic effect of morphine + GBP. These results and the good tolerability of GBP should favor clinical trials investigating the clinical relevance of the combination of morphine and GBP for treating severe pain.

IMPLICATIONS: In a randomized, placebo-controlled, double-blinded trial with 12 healthy volunteers, we studied the interaction of morphine and gabapentin using the cold pressor test. The anticonvulsant gabapentin enhanced the acute analgesic effect of morphine. Furthermore, the plasma concentration of gabapentin was increased when morphine was administered concomitantly. Therefore, the well tolerated combination of gabapentin and morphine may improve pain therapy, especially in pain states, like chronic and neuropathic pain, which respond poorly to opioids.

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