Analgesic action of i.v. morphine-6-glucuronide in healthy volunteers

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The pharmacodynamics of morphine-6-glucuronide (M-6-G) i.v. were assessed in 12 healthy male volunteers in an open study. After a single bolus dose of M-6-G 5 mg i.v., we measured antinociceptive effects, using electrical and cold pain tests, and plasma concentrations of M-6-G, morphine-3-glucuronide (M-3-G) and morphine. Pain intensities during electrical stimulation (at 30, 60 and 90 min after injection) and ice water immersion (at 60 min) decreased significantly ($P<0.005$) compared with baseline. Mean plasma peak concentrations of M-6-G were 139.3 (SD 38.9) ng ml^{-1}, measured at 15 min. Our data demonstrate that M-6-G has significant analgesic activity.

The major metabolites of morphine are morphine-6-glucuronide (M-6-G) and morphine-3-glucuronide (M-3-G).[1] M-6-G has a 100-fold higher affinity for μ opioid receptors compared with morphine when given intrathecally, and shows analgesic activity.[2] Systemic M-6-G has been shown to be approximately equipotent to morphine with respect to analgesic activity but with fewer side effects.[2] However, a recent study failed to demonstrate analgesic activity of M-6-G i.v. in healthy volunteers.[3] In this study, we have examined the analgesic activity of M-6-G i.v. in human volunteers using opioid sensitive pain tests, and related this to plasma concentrations.

Methods and results

After obtaining approved from the Ethics Committee of the University of Berne and written informed consent, we studied 12 healthy male volunteers (aged 21–46 yr, weight 53–80 kg) in an open study. Before injection of M-6-G, a baseline blood sample was obtained from the right antecubital vein and control pain tests conducted. After a light standardized meal, M-6-G 5 mg (Lipomed, Allschwil, Switzerland; >98.5% HPLC purity), dissolved shortly before use in sterile isotonic saline 5 ml, was injected as an i.v. bolus dose over 1 min. Blood samples were obtained every 15 min for the first 2 h and then hourly until the end of the study (5 h). One subject received M-6-G 10 mg and another subject 20 mg orally.

Subjects were instructed in detail concerning the pain tests and a practice run was performed before actual data collection. During testing, subjects were in a quiet, warm room, in a comfortable sitting position. Two standardized tests were performed. In the ice bucket pain test, the non-dominant hand was immersed in an ice water bath maintained at a constant temperature of 4°C and pain intensity was noted after 170 s on a 100-mm visual analogue scale (VAS; 0=no pain, 100=unbearable pain). In the electrical pain stimulation test, the pain tolerance threshold was determined by increasing the current applied with an electrical nerve stimulator (100 Hz tetanic stimulation, Digistim, Biometer A/S, Copenhagen, Denmark) to the thenar eminence of the dominant hand by 0.1 mA s^{-1} until the pain sensation became 'intolerable'. Prior reduction of skin resistance was ensured by degreasing and scrubbing the skin with emery paper. The tolerance threshold current was applied on two occasions for 30 s and pain scores were noted on a VAS. Both pain tests were performed 10 min before and 30, 60, 90, 120, 180 and 300 min after injection of M-6-G. Side effects were noted.
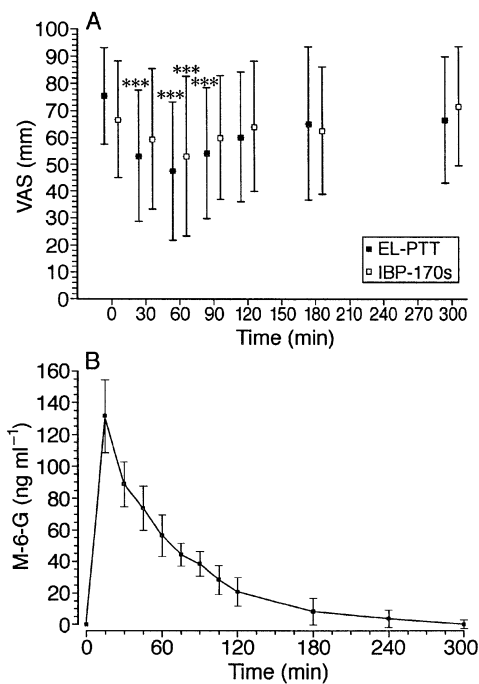
Fig 1 Antinociceptive effects and plasma concentrations of M-6-G. A: Mean (SD) visual analogue pain scores (VAS) of pain intensity (0=no pain, 100=unbearable pain) during ice bucket immersion and electrical stimulation at 200% pain tolerance thresholds in 12 healthy volunteers. EL-PTT=Electrical pain tolerance thresholds, IBP-170s=ice bucket pain test lasting 170 s. ***P<0.001 *vs* pre-M-6-G baseline. B: Mean (SD) plasma concentrations of morphine-6- glucuronide (M-6-G).

Statistical analysis was performed using analysis of variance (ANOVA) and *post hoc* Tukey's honest significance test. *P*<0.05 was considered significant.

Concentrations of M-6-G, M-3-G and morphine in plasma were assayed by high-pressure liquid chromatography with diode-array detection (HPLC-DAD).[4]

All 12 volunteers completed the pain tests. There were no serious or objective side effects. Subjective effects were sensations of heaviness, warmth and faster pulse (12 of 12 subjects), nervousness (seven), shortness of breath (three) and localized rash (three).

The time–effect for pain intensities during both the ice bucket and electrical pain tests was highly significant (*P*<0.0001) (Fig. 1A). Pain intensities during electrical stimulation were significantly lower than baseline at 30, 60 and 90 min after administration of M-6-G (*P*<0.0005). With the ice bucket test, pain intensity at 60 min was significantly lower than that at baseline (*P*=0.004). At other times differences were not significant. In two subjects who received oral M-6-G, no effects on nociception were observed.

M-6-G was present in plasma only after i.v. administration. Peak plasma concentrations of M-6-G of 90–228 ng ml^{-1} (mean 139.3 (SD 38.9) ng ml^{-1}) were measured at 15 min (Fig. 1B). Morphine was not detectable.

Comment

We have demonstrated that M-6-G has analgesic activity in human volunteers after i.v. application when appropriate and sensitive pain tests are used, corroborating earlier studies in patients and healthy subjects.[2] In contrast, a recent placebo- and morphine-controlled study[3] reported a lack of analgesic activity after constant infusion of M-6-G, although steady-state M-6-G plasma concentrations (70–175 ng ml^{-1}) were similar to those in our study (90–228 ng ml^{-1}). However, the study of Loetsch and colleagues[3] must be interpreted with caution because of the very high incidence of opioid effects and use of naloxone and antiemetics almost exclusively in the morphine group. The resultant unblinding may have prejudiced volunteer reactions and it is possible that the rescue medication itself had effects on nociception. Moreover, the pain-evoked cerebral late potentials used in their study are recognized to be multifactorial in origin and cannot be assumed to measure sensory discriminative responses to pain, but rather reflect emotional–motivational aspects of pain.[5] Late potentials of this type are particularly sensitive to non-analgesic sedation, as seen in the morphine but not in the M-6-G or placebo groups in the study of Loetsch and colleagues.

Because of the difficulties of true blinding in opioid medication groups, we chose an open study design. The choice of tests for demonstration of opioid analgesia is crucial, as phasic, mainly A-δ fibre activating stimuli, as used by Loetsch and colleagues, have been shown to be insensitive for this purpose.[6] The tonic and suprathreshold pain tolerance tests in our study were chosen to ensure activation of C-fibres sensitive to opioid effects. Although qualitative responses to electrical and cold pain stimulation were similar, the former is a multimodal stimulus and the latter probably monomodal. Clinical studies with patients are now necessary to further evaluate the therapeutic potential of M-6-G.

Acknowledgements

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