

## Preemptive Intravenous Morphine-6-glucuronide Is Ineffective for Postoperative Pain Relief

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**Background:** Morphine-6-glucuronide (M-6-G), a major metabolite of morphine, is reported to be more potent than morphine when administered intrathecally; however, its efficiency remains under debate when administered intravenously. This study was designed to assess the analgesic efficiency of intravenous M-6-G for the treatment of acute postoperative pain.

**Methods:** After informed consent was obtained, 37 adults (American Society of Anesthesiologists physical status I-II) who were scheduled for elective open knee surgery were enrolled in the study. General anesthesia was induced with thiopental, alfentanil, and vecuronium and was maintained with a mixture of nitrous oxide/isoflurane and bolus doses of alfentanil. At skin closure, patients were randomized into three groups: (1) morphine group ( $n = 13$ ), which received morphine 0.15 mg/kg; (2) M-6-G group ( $n = 12$ ), which received M-6-G 0.1 mg/kg; and (3) placebo group ( $n = 12$ ), which received saline. At the time of extubation, plasma concentration of morphine and M-6-G was measured. Postoperative analgesic efficiency was assessed by the cumulative dose of morphine delivered by patient-controlled analgesia. Opioid-related side effects were also evaluated.

**Results:** No difference was noted in patient characteristics and opioid-related side effects. Morphine requirements (mean  $\pm$  SD) during the first 24 h in the M-6-G group ( $41 \pm 9$  mg) and the

placebo group ( $49 \pm 8$  mg) were significantly greater ( $P < 0.05$ ) compared with the morphine group ( $29 \pm 8$  mg).

**Conclusion:** A single intravenous bolus dose of M-6-G was found to be ineffective in the treatment of acute postoperative pain. This might be related to the low permeability of the blood-brain barrier for M-6-G. (Key words: Morphine; postoperative pain management.)

MORPHINE-6-GLUCURONIDE (M-6-G) is a metabolite of morphine with potent analgesic effect.<sup>1</sup> M-6-G has opioid receptor subtype binding affinities similar to those of morphine<sup>2,3</sup> and, after systemic administration to rodents, is onefold to fourfold more potent than morphine<sup>3-8</sup> and up to several hundred-fold more potent than morphine when administered by intracerebroventricular route.<sup>3-6,9-12</sup> M-6-G was reported to contribute to both analgesic and side effects of morphine in humans.<sup>13,14</sup> In addition, in patients with renal failure, morphine toxicity was attributed to M-6-G because, in contrast to morphine, this metabolite accumulates in the plasma<sup>15-18</sup> and cerebrospinal fluid<sup>19</sup> of those patients. Analgesic action of M-6-G in humans is still under debate. When compared with intrathecal morphine, intrathecal M-6-G reduces the dose of meperidine necessary to control severe pain of cancer patients.<sup>20</sup> M-6-G, 0.1 mg administered intrathecally, was at least as potent as 0.5 mg morphine administered intrathecally to control postoperative pain after total hip prosthesis.<sup>21</sup> The effects of parenteral M-6-G are subject to controversies. Sedation with fewer side effects than morphine and reduced ventilatory response to carbon dioxide was reported in volunteers after injection of 30 or 60  $\mu$ g/kg M-6-G.<sup>22,23</sup> Analgesia has also been described in patients with cancer pain after a single intravenous administration of M-6-G.<sup>24</sup> However, a recent double-blind, randomized study showed that intravenous M-6-G (6 mg for 70 kg) lacked analgesic activity in volunteers.<sup>25</sup>

We decided to evaluate the effect of intravenous M-6-G given preemptively to treat postoperative pain in patients undergoing open knee surgery during general anesthesia.

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Because M-6-G is known to cross the blood-brain barrier slowly,<sup>26-28</sup> it was administered preemptively, before the outbreak of pain. The study was controlled using morphine and placebo treatments as control groups. Patient-controlled analgesia (PCA) with morphine was used postoperatively, and analgesic effect was mainly assessed from the postoperative morphine consumption and pain scores.

## Methods

The local ethical committee for human research approved the study, and written informed consent was obtained from all patients. Thirty-seven consecutive patients (American Society of Anesthesiologists physical status I-II) aged 20–75 yr and scheduled for elective open knee surgery (total knee prosthesis, tibial osteotomy, or ligamentoplasty) during general anesthesia were enrolled in the study. Exclusion criteria were obesity (> 30% ideal body weight), chronic pain medication, and preoperative pain at rest. The day before surgery, adequate explanation was given to the patient regarding use of a PCA pump and the 0- to 100-mm visual analog scale for assessment of postoperative pain. General anesthesia was induced with thiopental 5–7 mg/kg and alfentanil 20–30 µg/kg, and vecuronium 0.1 mg/kg to facilitate tracheal intubation. The lungs were ventilated to normocapnia while anesthesia was maintained with a mixture of N<sub>2</sub>O–O<sub>2</sub> (60/40%) and isoflurane at an end-tidal concentration of 0.8–1.1%. When needed, analgesia was maintained with bolus doses of alfentanil (500–1,000 µg). Active forced air warming was used to maintain normothermia. At the beginning of skin closure, patients were assigned randomly using a computer-generated random-number sequence to receive a single intravenous injection of morphine sulfate 0.15 mg/kg (morphine group), a single injection of M-6-G 0.1 mg/kg (M-6-G group), or an injection of saline (placebo group). The anesthetist in charge of the patient was not aware of the randomization.

Morphine-6-glucuronide was provided as a sterile powder by Ehrenstorfer-Schäfers Laboratory (Augsburg, Germany). M-6-G was dissolved in sterile water and stored at 4°C in ampules, each containing 2 ml of a 5-mg/ml solution of M-6-G. The purity of M-6-G was controlled by high-pressure liquid chromatographic analysis of the M-6-G powder using morphine-6 β-glucuronide (Sigma-Aldrich, L'Isle D'Abeau, Chesnes, Saint Quentin, France) as reference. The potency of the M-6-G solution had been checked by assessing the effect of an intrathecal

administration of M-6-G in comparison to morphine on the C-fiber reflex in the rat.<sup>29,30</sup> A dose of 40 ng M-6-G administered intrathecally completely inhibited the C-fiber reflex, and this effect was reversed by naloxone 0.4 mg/kg administered intravenously. Compared with morphine,<sup>29,30</sup> M-6-G administered intrathecally was estimated to be at least 40 times as potent.

At the end of the procedure, patients were transferred to the recovery room and extubated once adequate clinical recovery occurred. Immediately after extubation and before any further injection of morphine, a sample of venous blood (5 ml in a heparinized tube) was withdrawn. Blood was centrifuged immediately, and plasma was maintained at –20°C. Plasma samples were assayed for morphine and M-6-G.<sup>31</sup>

The following parameters were assessed for the first 6 consecutive h: (1) pain scores at fixed intervals after extubation (0, 15, 30, 45, 60, 90, and 120 min, and 4, 6, and 24 h); (2) morphine requirements (time between study drug administration and first demand, the necessity of intravenous titration, and cumulative amounts during the first 6 h in the recovery room and at 24 h). Initially, intravenous morphine was titrated if the visual analog scale pain score was > 50 mm. Once a score of < 50 mm was achieved, morphine was delivered by a PCA pump with bolus doses of 1 mg, a lock-out period of 7 min, and a maximal permitted dose of 20 mg for 4 h. Additional bolus doses of morphine were permitted in the recovery room. In the surgical ward, if the maximum-permitted dose of morphine was reached, paracetamol and nonsteroidal antiinflammatory drugs were administered. The times between the last administration of alfentanil, the first assessment of pain, and the first morphine administration and the time between extubation and the first morphine administration were recorded. Opioid-related adverse effects such as urinary retention necessitating bladder catheterization, nausea and vomiting, and pruritus were recorded. Pulse oximetry (Sp<sub>O</sub><sub>2</sub>) was monitored continuously during the first 24 h. Supplementary oxygen was administered to every patient in the recovery room. In the surgical ward, oxygen was given if oxygen saturation decreased to < 90% for > 2 min. The PCA pump was withdrawn and the patient was excluded from the study if heavy sedation, Sp<sub>O</sub><sub>2</sub> < 90% with nasal oxygen, or a respiratory rate < 10 breaths/min occurred.

### Statistical Analysis

The sample size was determined on the basis of an expected difference in the mean morphine consumption

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**Table 1. Patients Characteristics and Surgical Events**

	Morphine (n = 13)	M-6-G (n = 11)	Placebo (n = 13)	P Value
Age (yr)	55 ± 15	60 ± 13	63 ± 11	0.3
Weight (kg)	73 ± 11	77 ± 12	73 ± 13	0.9
Height (cm)	163 ± 7	164 ± 10	163 ± 6	0.9
Sex (M/F)	(5/8)	(3/8)	(2/11)	0.2
ASA (I/II)	(7/6)	(3/8)	(7/6)	0.2
Thiopental (mg)	488 ± 50	509 ± 106	492 ± 93	0.6
Alfentanil (μg)	4461 ± 1676	3636 ± 1142	4269 ± 2175	0.6
Type of surgery (P/T/L)	(5/7/1)	(5/5/1)	(9/4/0)	0.3
Duration of anesthesia (min)	181 ± 86	165 ± 57	221 ± 67	0.19
Duration of surgery (min)	150 ± 67	126 ± 51	185 ± 55	0.07
Time to extubation (min)	50 ± 19	51 ± 35	54 ± 27	0.9

Values are mean ± SD when expressed.

\* P/T/L refers to knee prosthesis, tibial osteotomy, and ligamentoplasty, respectively.

of 10 mg and an SD of 7.5 mg with  $\alpha = 0.05$  and  $\beta = 0.8$ . Data were analyzed using Statistica version 5.0A software (Stat Soft Inc., Tulsa, OK). Analysis of variance or Kruskal-Wallis analysis of variance were used to compare patient characteristics, amount of anesthetics, duration of anesthesia, duration of surgery, time to extubation, and times to first morphine demand. Two-way repeated measures of analysis of variance followed by the protected least significant difference Fisher exact test for *post hoc* analysis were used to compare morphine consumption and visual analog scale pain score. When adequate, Fisher exact and chi-square tests were used for categorical data.

## Results

No statistically significant difference was noticed between the groups for patients characteristics, anesthetics requirements, type of surgery, and time of extubation (table 1). In the M-6-G group, the plasma concentration

of M-6-G averaged  $450 \pm 140$  nM 55 min after its administration (table 2). No morphine was detected in the plasma of patients in the M-6-G group. Morphine requirements from 15 min after extubation until the end of the study period were significantly higher ( $P < 0.05$ ) in the placebo group ( $49 \pm 8$  mg) and the M-6-G group ( $41 \pm 9$  mg) than in the morphine group ( $29 \pm 8$  mg; fig. 1). The time between administration of the study drug and the first demand for analgesia was significantly shorter ( $P < 0.01$ ) in the M-6-G and the placebo groups compared with the morphine group (table 2). The time between extubation and the first morphine administration was shorter ( $P < 0.01$ ) in the M-6-G and the placebo groups compared with the morphine group. The pain scores at admission in the recovery room were significantly lower in the morphine group than in the other two groups ( $P < 0.05$ ; fig. 2). No significant difference in pain scores between the groups was observed after a period of 30 min until the end of the assessment. In two patients, the total consumption of morphine over 24 h

**Table 2. Postoperative Data: Morphine and M-6-G Dosage, Timing, and Opioid-Related Side Effects**

	Morphine (n = 13)	M-6-G (n = 11)	Placebo (n = 13)	P
Plasma concentration of M-6-G (nM)	30 ± 9	450 ± 140	0	NA
Plasma concentration of morphine (nM)	22 ± 6	0	0	NA
Time from last alfentanil administration to first pain assessment (min)	92 ± 31	87 ± 60	113 ± 30	0.3
Time between last alfentanil administration to first morphine injection (min)	186 ± 100	131 ± 61	157 ± 60	0.2
Time between study drug injection and first morphine administration (min)	100 ± 30	62 ± 26	68 ± 29	0.004
Time between extubation and first morphine administration (min)	66 ± 64	20 ± 17	21 ± 18	0.007
Necessity to titrate (y/n)	5/8	8/3	11/2	0.2
Nasal oxygen in surgical ward (y/n)	7/6	6/5	6/7	0.9
Nausea and vomiting (y/n)	8/5	3/8	4/9	0.4
Pruritus (y/n)	1/12	2/9	2/11	0.7
Bladder catheterization (y/n)	3/10	3/8	3/11	0.8

Values are mean ± SD when expressed, values between parenthesis are the number of patients.

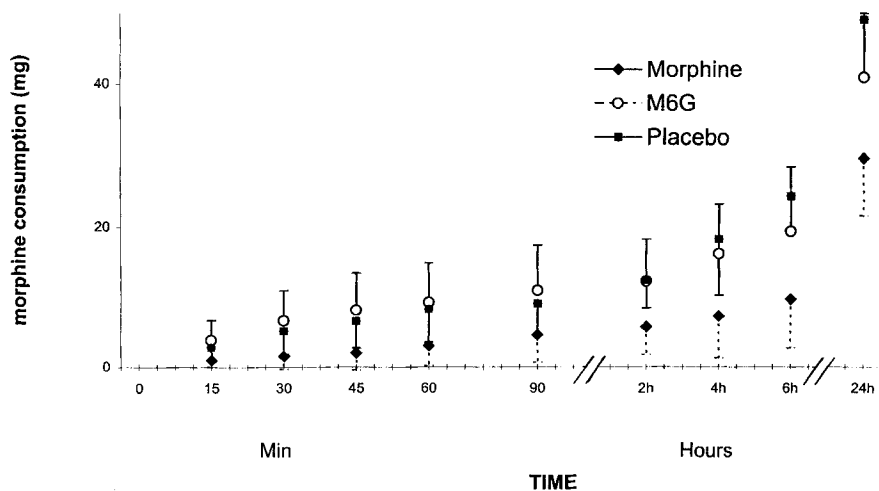


Fig. 1. Time-effect curve for postoperative morphine requirements during the 24-h observation period. Mean morphine consumption ( $\pm$  SD) are plotted versus time. \*Two-way repeated measures of analysis of variance (group and time):  $P = 0.000002$ ,  $F = 12.66$ ,  $df = 2$  for the group factor, whereas  $P = 0.0000001$ ,  $F = 185$ ,  $df = 9$  for the time factor. For *post hoc* intergroup analysis, the protected least significant difference test was used:  $P = 0.0004$  for the morphine vs. placebo groups,  $P = 0.0005$  for the morphine vs. M-6-G groups, and  $P = 0.66$  for the M-6-G vs. placebo groups. The protected least squares difference test at each time point showed that the  $P$  value was  $< 0.05$  between the placebo and morphine groups and between the placebo and M-6-G groups during the total study observation, whereas the  $P$  value was always  $> 0.05$  for comparison between the placebo and M-6-G groups.

could not be assessed. The first patient, who was in the placebo group, was a 69-yr-old woman who had a respiratory rate of 6 breaths/min and was heavily sedated at the seventh postoperative hour. In the recovery room, she had received an accumulated dose of 23 mg morphine. She woke up after receiving 0.4 mg naloxone, and her respiratory rate increased to 14 breaths/min. The second patient, who was in the morphine group, was a 72-yr-old woman who received 6 mg morphine by PCA pump and remained very sleepy during her stay in the recovery room. Intravenous nonopioid analgesia was administered, and the PCA pump was removed until she became wide awake. No difference was noticed between groups in terms of opioid-related side effects.

## Discussion

In the present study, we were unable to demonstrate an analgesic effect of intravenously administered M-6-G. Pain score in the early phase of recovery and the dose of morphine necessary for pain relief were similar in the M-6-G and placebo groups. These results confirm the results of the previous study in volunteers<sup>25</sup> but contradict the previous reports of an analgesic action of intravenous M-6-G in patients with cancer pain.<sup>24</sup>

Compared with the study by Löttsch *et al.* in volunteers,<sup>25</sup> the doses of M-6-G administered (6 mg for 70 kg) were similar, although M-6-G was given as a continuous infusion instead of a single injection, as in our study.

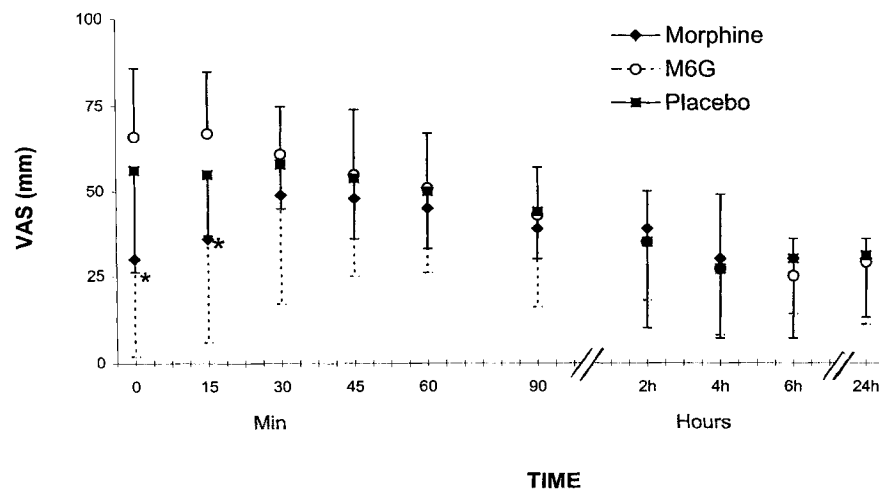


Fig. 2. Time-effect curve for postoperative pain scores from extubation time (EXT) until the 24th postoperative hour. Mean visual analog scale scores ( $\pm$  SD) are plotted against time. Pain scores were significantly lower in the morphine group from extubation to 30 min. Two-way repeated measures of analysis of variance (group and time):  $P = 0.02$ ,  $F = 4.3$ ,  $df = 2$  for the group factor, protected least significant difference test was used for *post hoc* analysis;  $P = 0.03$  between the placebo and morphine groups,  $P = 0.008$  between the morphine and M-6-G groups, and no difference was noted between the placebo and M-6-G groups ( $P = 0.6$ ). From 30 min until the end of the observation period, no statistically significant difference was noted between groups, and pain scores significantly decreased during the study period within each group (time factor):  $P = 0.0000001$ ,  $F = 20$ ,  $df = 9$ .

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Both studies were randomized and double-blinded and compared M-6-G to a placebo and a positive control (morphine). In the study by Lötsch *et al.*,<sup>25</sup> pain-related parameters were assessed 3.5 h after the start of the infusion. The main difference is that in our study, we evaluated the analgesic effect on postoperative pain, with pain after knee surgery being considered as a model of severe acute pain, whereas in the study by Lötsch *et al.*,<sup>25</sup> an experimental model of noxious stimuli was used. The assessment of an analgesic effect on spontaneous elicited pain such as acute postoperative pain is clinically more relevant than an experimental model of pain induced by noxious stimuli.<sup>32</sup> Because M-6-G is known to cross the blood-brain barrier slowly,<sup>19</sup> it is not conceivable that any rapid relief of pain will occur with this compound. Therefore, M-6-G was administered preemptively, before recovery from anesthesia. In patients with cancer pain, Osborne *et al.*<sup>24</sup> reported that doses between 0.5 and 4 mg of intravenous M-6-G were effective in producing pain relief, and no correlation was found between the dose or the plasma concentration of M-6-G and the degree of analgesia. Also surprising was the development of pain relief as soon as 15 min after intravenous M-6-G administration.<sup>24</sup> Sedation and reduced ventilatory response to carbon dioxide were also observed 20 min after intravenous administration of 60  $\mu\text{g}/\text{kg}$  M-6-G.<sup>22,23</sup> These discrepancies may be explained, in part, by the study design, because some studies were not randomized.<sup>22,24</sup> Differences between studies may also be a result of differences in the compound studied, which had been provided by different manufacturers. In the current study, the purity and stability of the compound studied was verified by chemical analysis, and furthermore, no breakdown of M-6-G into morphine could be detected from plasma analysis. Therefore, only potential effects of M-6-G itself were assessed in the present study. In addition, the potent analgesic effect of our M-6-G batch was checked on an animal model. In the present study, alfentanil was used intraoperatively as analgesic, but it is unlikely that it contributes to postoperative analgesia because of its short elimination half-life<sup>33</sup> and the fact that the last dose of alfentanil was administered 90 min before tracheal extubation. In addition, in the placebo group, as in the M-6-G group, pain scores were initially high, suggesting the absence of a residual effect of alfentanil.

From the results of the present study, we do not exclude that M-6-G may exert an analgesic effect in humans. It can be argued that the decline in the plasma concentration after an intravenous bolus dose of M-6-G is

too fast to allow sufficient time for transfer across the blood-brain barrier because M-6-G shows a poor blood-brain permeability.<sup>19</sup> We agree that a continuous infusion of M-6-G over 4 h (Lötsch *et al.*<sup>25</sup>) may be a more favorable regimen for the transfer of M-6-G into the brain compared with an intravenous bolus dose. However, the dose of 0.1 mg/kg M-6-G administered in the current study is a relatively large dose compared with those in previous studies.<sup>22-24</sup> In the current study, the plasma concentration of M-6-G averaged 450 nM 50 min after an intravenous bolus dose, which fitted well with the predicted value derived from the pharmacokinetic model of M-6-G.<sup>34</sup> In comparison with the plasma concentration of M-6-G measured by Lötsch *et al.*<sup>25</sup> after a different regimen of continuous administration of M-6-G, we assume that the plasma concentrations of M-6-G achieved are within the same range of values during the first 2 h after an intravenous bolus dose of 0.1 mg/kg M-6-G.

In summary, this study suggests that M-6-G administered preemptively as an intravenous bolus dose will be of little clinical interest in the treatment of acute postoperative pain.

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