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Randomized, Double-blind Study of the Analgesic Efficacy of Morphine-6-Glucuronide versus *Morphine Sulfate for Postoperative Pain in Major Surgery*

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Background: **Morphine-6-glucuronide (M6G) has promising preclinical characteristics and encouraging pharmacokinetic features for acute nociceptive pain. Early studies have produced a good safety profile when compared to morphine sulfate, although in surrogate pain models studies, a mixed picture emerged. A study to evaluate the efficacy and safety profile in a clinical setting was designed.**

Methods: **The authors conducted a double-blind, randomized, dose-finding study of patients scheduled to undergo major joint replacement. One hundred patients of both sexes were included, with 50 patients in each group. A loading dose of 10 mg of study medication was given intravenously at induction of anesthesia, and two further doses were allowed during surgery if required. Bolus doses *via* a patient-controlled analgesia system were given subcutaneously at 2 mg/dose and set at a 10-min lockout. Assessments of pain intensity and relief were recorded during the 24-h period.**

Results: **There were no statistically significant differences between the treatments for 24-h mean pain intensity. However, pain intensity was significantly higher in the M6G group than in the morphine group at 30 min and 1 h. There was no statistical difference in 24-h mean pain relief or retrospective pain scores at any time point during the 24-h period. The severity of sedation was significantly greater in the morphine group than in the M6G group at 30 min, 1 h, 2 h, and 24 h. Respiratory depression was greater in the morphine group than in the M6G group, and more patients in the morphine group withdrew from the study because of respiratory depression.**

Conclusions: **Overall, M6G has an analgesic effect similar to that of morphine over the first 24 h postoperatively. However, M6G may be slower onset initially than morphine; therefore, a larger initial dose may be required.**

BEFORE the 1970s, it was generally believed that morphine glucuronides were pharmacologically inactive and that their formation was a mechanism for the detoxification and elimination of the parent compound *via* urine and bile. It is now recognized that their formation has important pharmacologic and toxicologic implications. After the first reports[1] that morphine-6-glucuronide (M6G) has significant antinociceptive activity in animals, an intense interest was generated for its possible use as an analgesic, particularly one without the undesirable side effects of morphine.

Preclinical studies have confirmed a strong antinociceptive effect of M6G, although the potency relative to morphine varies according to the route of administration. M6G was slightly more potent than morphine after intravenous or subcutaneous administration (1.5:1), and it was significantly more potent when injected centrally (100:1).[2–5] M6G binds to opioid receptors across many species (mouse, rat, guinea pig, rabbit, and cow).[6–10] It has been reported that morphine has some differences in its affinity for opioid receptor subtypes, which may explain the better safety profile of M6G.[11,12]

Studies conducted in humans have produced mixed results. In human pain models, some investigators found no appreciable analgesic effect of M6G, whereas others reported profound analgesia and less adverse effects when compared with morphine.[13–16]

Clinical studies in patients with nociceptive pain produced direct evidence for the analgesic effect of M6G, although the numbers of patients were small.[17,18] However, to underpin any claims of a superior therapeutic index, appropriate clinical trials must be undertaken to compare the analgesic efficacy and the incidence and severity of side effects against an accepted standard.

The purpose of this study was to assess the analgesic effect of M6G after major joint replacement and to compare these effects to those of morphine in a randomized, double-blind format.[19]

Materials and Methods

The study was reviewed and approved by the King's College, London Research Ethics committee. Patients were given full verbal and written explanation of the study, and an informed written consent form was obtained before inclusion in the study. The trial was conducted in accordance with Good Clinical Practice Guidelines (CPMP/ICH/135/95)[20] and was independently monitored.

This was a randomized, double-blind, comparator-controlled, parallel, two-group study. One hundred patients of both sexes, scheduled to undergo major joint replacements, including revisions, were evaluated for inclusion in the study (table 1). If a patient fulfilled the entry criteria, the patient's complete demographic information was collected. Information about the patient's med-

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Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Scheduled to undergo major joint replacement surgery	• Analgesics other than diclofenac (short-acting 50 mg) 24 h before surgery
• Male or female and aged between 18 and 75 yr	• Administration of monoamine oxidase inhibitors, neuroleptics, benzodiazepines, or barbiturates
• Weight between 50 and 90 kg	• Systemic disorders that may interfere with absorption, distribution, metabolism, or excretion including severe liver or renal disease (total bilirubin >40 μM, S-creatinine >150 μM
• Written informed consent after both oral and written information has been given	• Severe asthma or other chronic pulmonary diseases
	• Hypersensitivity or allergy to morphine or other narcotic analgesics
	• Administration of any investigational drug within the past 30 days apart from low-molecular-weight heparin
	• History of drug abuse, alcohol abuse, or major psychiatric disorders
	• Patients who do not wish to participate

ical history and the medicine consumption was obtained. A physical examination and clinical chemistry testing were also performed. Eligible patients who provided informed consent were randomly assigned to receive either M6G or morphine sulfate.

Only 50 mg of diclofenac was permitted within 24 h before the surgery. Patients were allowed to take their current analgesic medication up to 24 h preoperatively. Codeine-containing medications were not permitted within 24 h before surgery. From 12 h to 4 h before surgery, patients were allowed to take paracetamol (two tablets every 6 h) or coproxamol (325 mg paracetamol, 32.5 mg dextropropoxyphene per tablet). No analgesics were permitted within 4 h before surgery. Patients were allowed to take up to 20 mg temazepam the night before the operation.

Patients were anesthetized using standard anesthesia with premedication of 20 mg temazepam, 200 mg propofol, one loading dose of study medication (10 mg M6G or morphine, intravenously), and atracurium. Maintenance was with isoflurane and 50.0% nitrous oxide and 50.0% oxygen; reversal was with neostigmine and atropine.

During surgery, two extra 10-mg doses could be given if the patient showed signs of intraoperative pain (*e.g.*, tachycardia, hypertension, sweating) in the presence of adequate anesthesia, full paralysis, normocapnia, and adequate oxygenation.

No antiemetic was given prophylactically, and if the patient reported nausea postoperatively, 12.5 mg intramuscular prochlorperazine was given. Nonsteroidal antiinflammatory agents and local anesthetic blockade were not allowed.

Postoperatively, patients were nursed in an area with full resuscitation facilities and with nursing and medical staff who were skilled in advanced resuscitation techniques. Because of the possibility of respiratory depression (respiration rate of < 8 breaths/min or reduced oxygen saturation [< 90%]; naloxone in a dose of 200–400 μg was available intravenously). Study medication of M6G or morphine was administered *via* the patient-controlled analgesia (PCA) system containing study medication given as 2-mg subcutaneous bolus doses, with a 10-min lockout period after each dose. The maximum dose in any 4-h period was 48 mg.

The PCA device was used subcutaneously, the usual practice at King's College. This is also based on pharmacokinetic studies undertaken at King's College, where it was shown that the bioavailability of subcutaneous morphine was equal to that of intravenous morphine, and on institutional audit, subcutaneous administration was considered to offer significantly fewer adverse side effects than the intravenous route.

If sufficient pain relief was not achieved with the dosing regimen, the patient was given alternative analgesia and withdrawn from the study.

Statistical Methods

Sample Size. The sample size calculation was based on detecting a difference of at least 20% between the treatments in mean pain intensity. Assuming a power of 80%, a level of significance of 5%, a coefficient of variation of 29.5% (taken from a previous pilot study), and a dropout rate of 30%, it was estimated that 100 patients would be required, 50 in each treatment group.

The primary population for the efficacy analysis was efficacy. The analyses of pain intensity and pain relief were to be performed with and without the last-observation-carried-forward approach to impute missing observations.

Mean pain intensity and PCA demanded doses were to be summarized by treatment group, and between-treatment comparisons were to be performed using analysis of covariance, adjusting for baseline pain intensity. The assumption of normality was to be checked, and if the assumption was not upheld, between-treatment comparisons were to be performed using the Cochran-Mantel-Haenszel test, stratified by baseline pain intensity. In addition, pain intensity was summarized and analyzed at each assessment time point, using the same methodol-

ogy as for mean pain intensity. Pain relief was to be treated as a continuous rather than a categorical variable, and analyses were to be performed as described for mean pain intensity. Retrospective pain was to be analyzed using the Cochran-Mantel-Haenszel test, stratified by baseline pain intensity. Severity of nausea and sedation was analyzed using the Mantel-Haenszel chi-square test. The incidences of nausea, vomiting, and sedation were analyzed using the Fisher exact test.

Efficacy Assessments

The primary endpoint was mean pain intensity, which was measured at baseline, 30 min, and 1, 2, 3, 4, 5, 6, 10, 12, and 24 h on an 11-point numeric rating scale. If a patient was asleep during the first 6 h, he or she was woken up for the assessments. Other parameters were considered secondary variables. Pain relief was measured using a five-point verbal rating scale at the same time points as pain intensity. Retrospective pain scores were measured at study termination using a six-point verbal rating scale. The total amount of study medication used in 4-h periods was measured.

Nausea, vomiting, and sedation were evaluated using a verbal rating scale at baseline, 30 min, and 1, 2, 3, 4, 5, 6, 10, 12, and 24 h. The time of any antiemetic requirement was recorded. Adverse events were reported in three ways: The event was observed by the investigator; the event was reported by the patient; or the patient was asked, by open question 24 h after having received the first dose, whether any adverse events had occurred. Hematologic and clinical chemistry parameters were tested at inclusion and 24 h postoperatively. If any clinically relevant deviations occurred, a follow-up test was performed. Male and female patients aged 18–80 yr were included. All patients were undergoing elective surgery during general anesthesia for hip or knee replacement.

Results

Efficacy

The treatment groups were comparable in terms of durations of anesthesia and surgery. The mean duration of anesthesia was 136.4 min (range, 80–222 min), and the mean duration of surgery was 107.3 min (range, 35–187 min). The types and doses of anesthetics used were also comparable across treatment groups. A total of 54 patients (67%) had hip replacements, and 27 (33%) had knee replacements. Of these, 76 (94%) were cemented, and 5 (6%) were uncemented. Only 3 patients (4%) had revisions.

The efficacy results focus on the summaries and analyses based on the efficacy population, with the last-observation-carried-forward approach used to impute missing values because these summaries and analyses account for patients who dropped out before 24 h and therefore have the least potential for bias. Of the 100 patients included in the trial population, 1 patient did not receive study medication. Therefore, 99 patients, 50 in the M6G group and 49 in the morphine group, were included in the safety analysis.

The efficacy population consisted of all patients who received at least one dose of study medication and who provided at least one postbaseline efficacy measure. This included 81 patients, 46 in the M6G group and 35 in the morphine group.

Efficacy Conclusions

There was no statistically significant difference between the treatments in terms of 24-h mean pain intensity after baseline; however, pain intensity was significantly higher in the M6G group than in the morphine group at 30 min and 1 h ($P = 0.035$ and $P = 0.039$, respectively).

There was no statistically significant difference between the treatments in terms of 24-h mean pain relief. However, pain relief was significantly better in the morphine group than in the M6G group at 30 min and 1 h ($P = 0.013$ and $P = 0.032$, respectively; table 2). There was no statistically significant difference between the treatments in terms of respective pain score at any time point during the 24 h. Median pain relief scores were 0.0 in the M6G group and 1.0 in the morphine group at both 30 min and 1 h after baseline (a score of 0 indicates no pain relief and a score of 1 indicates a little pain relief). These median scores are not adjusted for baseline pain intensity (figs. 1 and 2). There was no statistically significant difference between the treatments in terms of retrospective pain score.

PCA Dose

The total dose was the sum of the perioperative and postoperative loading doses and the overall demanded PCA dose. The perioperative doses were calculated separately for analyses and showed no differences between the two groups. The results of the PCA demanded dose analyses must be interpreted carefully because of the number of patients who withdrew during the study.

The PCA demand dose was significantly higher during the 0- to 4-h period in the M6G group (20.8 ± 14.8 *vs.* 8.3 ± 5.3 mg; $P = 0.001$), but there was no treatment group difference at any other time period up to 24 h for the efficacy population. The mean total PCA demanded dose was higher in the M6G group than in the morphine group, although this difference did not reach statistical significance (46.1 ± 41.0 *vs.* 26.9 ± 23.5 mg; $P = 0.062$). It should be noted that the between-patient total PCA demanded dose ranged from 0 to 168 mg (table 3).

The greatest number of withdrawals (for any reason) occurred in the period up to 4 h after baseline, with more withdrawals from the morphine group than the

Table 2. Summary of Pain Intensity

	M6G (n = 46)		Morphine Sulfate (n = 35)		Total (n = 81)	
	Pain Score	Change from Baseline	Pain Score	Change from Baseline	Pain Score	Change from Baseline
Baseline						
Mean	7.9		7.4		7.7	
SD	1.9					
Median	8.0		7.0			
30 min	2.0		1.9			
Mean	8.4	0.6	7.2	−0.2	7.9	0.2
SD	1.8	1.6	2.6	2.1	2.3	1.9
Median	9.0	0.0	8.0	0.0	8.0	0.0
2 h						
Mean	6.2	−1.6	5.5	−1.7	5.9	−1.6
SD	2.4	1.7	2.9	2.4	2.6	2.0
Median	6.0	−1.5	5.0	−2.0	6.0	−2.0
4 h						
Mean	4.9	−2.8	4.3	−3.0	4.6	−2.9
SD	3.0	2.4	2.0	2.2	2.6	2.3
Median	5.0	−3.0	4.0	−3.0	5.0	−3.0
6 h						
Mean	4.0	−3.7	3.0	−4.3	3.6	−3.9
SD	3.0	2.4	2.4	2.4	2.8	2.4
Median	5.0	−4.0	2.0	−4.0	3.0	−4.0
10 h						
Mean	3.2	−4.6	2.5	−4.9	2.9	−4.7
SD	2.6	2.8	2.8	3.0	2.7	2.9
Median	3.0	−5.0	2.0	−5.0	2.0	−5.0
12 h						
Mean	3.5	−4.2	2.4	−5.0	3.0	−4.6
SD	2.8	3.2	2.5	2.9	2.7	3.1
Median	3.5	−5.0	1.5	−5.0	2.0	−5.0
24 h						
Mean	3.4	−4.4	2.7	−4.6	3.1	−4.5
SD	3.0	3.1	2.2	3.1	2.7	3.1
Median	3.0	−5.0	2.0	−5.0	2.0	−5.0

M6G = morphine-6-glucuronide.

M6G group during this period (49% *vs.* 36% of patients withdrawn).

The mean study duration was 14.5 h in the M6G group, compared with 11.7 h in the morphine group, and the mean treatment duration was 12.8 h in the M6G group, compared with 9.6 h in the morphine group.

The treatment groups were comparable with regard to the number of loading doses received. The severity of sedation was greater with morphine than with M6G during the 24 h after baseline, with significantly greater severity of sedation with morphine than with M6G at 30 min ($P = 0.011$), 1 h ($P = 0.017$), and 2 h ($P = 0.010$) after baseline. At 30 min and 1 h after baseline, median sedation severity scores were 1.0 in the M6G group and 2.0 in the morphine group (a score of 1 indicates mild sedation, and a score of 2 indicates moderate sedation). Twenty-four hours after baseline, median sedation severity scores were 1.0 in the M6G group and 2.0 in the morphine group.

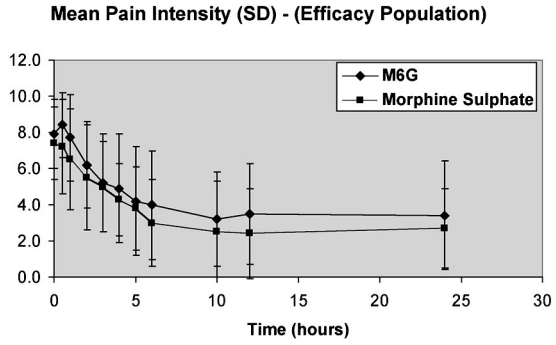

Fig. 1. Mean pain intensity (SD) (efficacy population). M6G = morphine-6-glucuronide.

Safety Evaluations

Nausea. There was no statistically significant difference between the treatments in terms of incidence or severity of nausea at any time during the 24 h after baseline. At any given time point during the 24 h after baseline, between 17% and 30% of patients who recorded a data point experienced nausea. The incidence of nausea was highest at the 24-h time point (6 patients [21%] in the M6G group and 9 patients [41%] in the morphine group). The median nausea severity score was 0.0 in both the M6G group and the morphine group at each assessment (a score of 0 indicates no nausea). There was no statistically significant difference between the treatments in terms of the incidence of vomiting at any time during the 24 h after baseline. The proportion of patients in each treatment group who experienced vomiting remained relatively constant during the first 6 h after baseline and then increased to a maximum at 24 h after baseline.

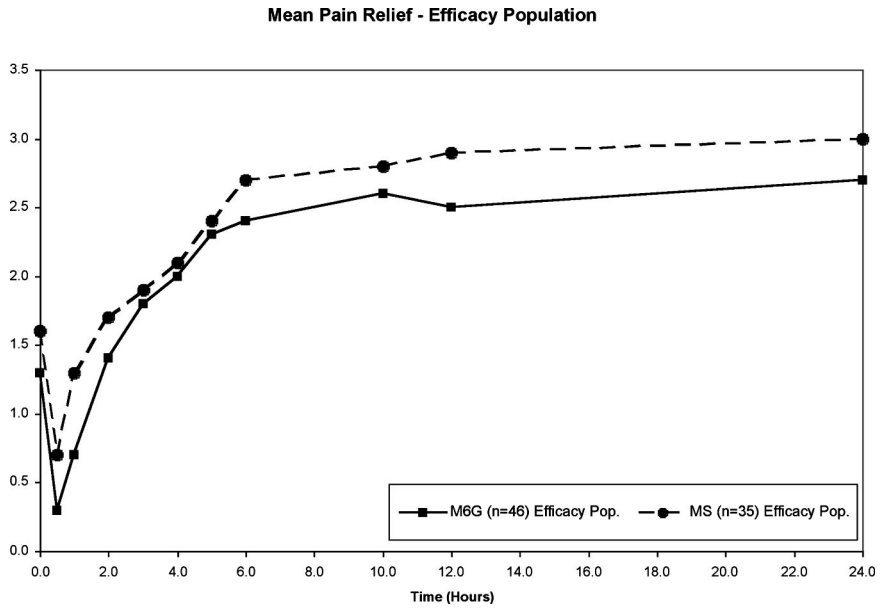

Fig. 2. Mean pain relief (efficacy population).

Withdrawal. A total of 82 patients (83%) received at least one postoperative loading dose of study medication, and 83 patients (84%) received at least one demanded PCA dose.

The greatest number of withdrawals (for any reason) occurred in the period up to 4 h after baseline, with more withdrawals from the morphine group than from the M6G group during this period (49% *vs.* 36% of patients withdrawn). The mean study durations were 14.5 h in the M6G group and 11.7 h in the morphine group, and the mean treatment durations were 12.8 h in the M6G group and 9.6 h in the morphine group.

Table 3. Exposure to Study Medication

	M6G (n = 46)	Morphine Sulfate (n = 35)	Total (n = 81)
No. of perioperative loading doses			
0	0	0	0
1	6 (13%)	6 (17%)	12 (15%)
2	26 (57%)	19 (54%)	45 (56%)
3	14 (30%)	10 (29%)	24 (30%)
Postoperative loading dose			
Yes	46 (100%)	35 (100%)	81 (100%)
No	0	0	0
At least one demanded PCA dose			
Yes	46 (100%)	32 (91%)	78 (96%)
No	0	3 (9%)	3 (4%)
Total demanded PCA dose, mg			
n	46	35	81
Mean	46.1	26.9	37.8
SD	41.0	23.5	35.7
Median	35.0	20.0	30.0
Minimum	2	0	0
Maximum	168	86	168
Total dose (loading doses and PCA doses), mg			
n	46	35	81
Mean	77.8	58.0	69.3
SD	38.6	24.4	34.5
Median	67.0	52.0	62.0
Minimum	26	28	26
Maximum	190	126	190

M6G = morphine-6-glucuronide; PCA = patient-controlled analgesia.

A total of 12 patients, 4 (8%) in the M6G group and 8 (16%) in the morphine group, were withdrawn from the study because of adverse events. Of these withdrawals, 9 (2 [4%] in the M6G group and 7 [14%] in the morphine group) were due to respiratory depression.

The proportion of patients who had respiratory depression as an adverse event or a treatment-related adverse event was higher in the morphine group (13 patients [27%]) compared with the M6G group (3 patients [6%]). There were no notable differences between the treatment groups in terms of the changes from baseline in pulse, systolic/diastolic blood pressure, or clinical chemistry. The majority of adverse events were considered to be related to study treatment.

Discussion

This study has confirmed that M6G has analgesic potency similar to that of morphine. However, it seems to have some clear differences. M6G may have a slower onset than morphine, or it may require a larger loading dose to initiate an effect, because the pain scores in the M6G group were higher than those in the morphine group at 30 and 60 min. This was also reflected in the pain relief scores, although over the 24-h period, the pain intensity and pain relief scores were similar in the two groups. Analyses of the pain scores and pain relief over time shows that both groups had very high baseline scores, and meaningful reduction in their pain scores was not accomplished for a

few hours.[21] There was a need for larger doses in both groups and smaller lockout times in the PCA program,[22] and because opioid requirements vary considerably from patient to patient, a rigid dosing program is unlikely to succeed.

The doses used were chosen as a result of a pilot study in which larger bolus doses of morphine produced a dropout rate of more than 50% as a result of adverse effects, particularly respiratory depression. The apparent initial slower onset of M6G could be a result of its being a hydrophilic compound, with its passage through the blood–brain barrier (BBB) likely to be slow and limited.[23] However, it has been shown that M6G exists in a conformational equilibrium, and therefore, if it is present in a lipophilic environment, it becomes more lipophilic itself.[24]

Studies on the rate of transport of morphine and M6G across the BBB have found M6G to be slower than morphine,[25] but a better explanation is the one offered by Stain-Texier *et al.*,[26] who found that M6G had a low BBB permeability but was associated with a high concentration in extracellular brain fluid and a longer elimination half-life. M6G may be slower to act, but it can provide better efficacy and a longer effect. It has been suggested the permeation of M6G across the BBB may be dependent on the expression of P-glycoprotein–mediated enzyme, which forms an outward transporter at the BBB.[27] A more recent study has indicated that there is evidence for an active transport for M6G but not P-glycoprotein–mediated transport.[28] It may be prudent to be aware that pain and inflammation could alter the function of the BBB, which may lead to changes in drug delivery to the brain. This factor was not taken into account in many of the above-mentioned studies.[29]

The use of the subcutaneous route for morphine has been satisfactorily used for postoperative pain management. It combines pharmacokinetics and efficacy that are similar to those of the intravenous route with the added simplicity of the route and greater patient acceptability.[30–33]

Full agonist opioids are the main agents used for moderate to severe pain, but their use is hampered by their safety profile. Life-threatening respiratory depression and somnolence are among the main factors that limit their utility.[34]

In this study, there were clear differences in the respiratory depression rates of the M6G and morphine groups. This was clear because the proportion of subjects with respiratory depression was markedly higher in the morphine group (13 patients [27%]) compared with the M6G group (3 patients [6%]), and 9 patients (2 [4%] in the M6G group and 7 [14%] in the morphine group) were withdrawn because of respiratory depression. Also, 17 patients (3 [6%] in the M6G group and 14 [29%] in the morphine group) had respiratory rates that decreased to below 8 breaths/min at one or more time points during the 24 h after baseline.

The data from this study support the previous impression that M6G has a better profile on respiration than morphine does.[12,35,36]

There was a clear difference in somnolence between the two groups, with significantly less sedation in the M6G group in the immediate postoperative period as well as at the end of the 24-h study period. It is sometimes assumed that sedation is synonymous with good pain control, but this is a myth. When patients awaken, their pain scores tend to be significant. This was recently confirmed in a postoperative study. A clear dissociation between sedation and pain relief does exist, and sedation tends to occur before analgesia.[37]

The above findings on adverse effects support the hypothesis that the affinity of M6G to opioid receptor subtypes is different than that of morphine. M6G binds to the μ_1 as well as the μ_2 receptor but has fourfold to fivefold lower binding affinity for the μ_2 receptor than morphine does. Mu-2 receptors are thought to be responsible for mediating respiratory depression, which could possibly explain the differences in the respiratory effect of M6G.[38]

There is also evidence to support a unique receptor that mediates the effects of M6G but not those of morphine, which may also play a part in explaining these differences.[39]

There were no differences in nausea and vomiting between the groups. This differs from findings of previous volunteer studies[11] and a recent day-surgery study. A study by Cann *et al.*[40] in which 144 women received either morphine or M6G as part of general anesthesia for day-case surgery found that M6G has a better safety profile than morphine.

Although it was not one of the primary aims of this study, it was possible to calculate the relative potency of M6G. The potency of morphine was found to be equal to that of M6G on a molar basis but higher on a milligram basis (morphine:M6G = 1:1.4). Two recent studies by Romberg *et al.*[12,41] have suggested that morphine is twice as potent as M6G, and a bolus dose of at least 0.2 mg/kg M6G is needed to induce analgesia. This could also explain previous negative studies that have used significantly smaller doses.

Overall, we can conclude that M6G is not the "Holy Grail"[34] for an opioid agonist because it does have opioid-related adverse effects. Nonetheless, it has a unique pharmacodynamic profile with a better therapeutic window than morphine. Its simple, clean pharmacokinetic characteristics[11] make it an attractive agent for further investigation in acute nociceptive pain.

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