REVIEW ARTICLE

Morphine-6-Glucuronide: Morphine's Successor for Postoperative Pain Relief?

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In searching for an analgesic with fewer side effects than morphine, examination of morphine's active metabolite, morphine-6-glucuronide (M6G), suggests that M6G is possibly such a drug. In contrast to morphine, M6G is not metabolized but excreted via the kidneys and exhibits enterohepatic cycling, as it is a substrate for multidrug resistance transporter proteins in the liver and intestines. M6G exhibits a delay in its analgesic effect (blood-effect site equilibration half-life 4–8 h), which is partly related to slow passage through the blood-brain barrier and distribution within the brain compartment. In humans, M6G's potency is just half of that of morphine. In clinical studies, M6G is well tolerated and produces adequate and long lasting postoperative analgesia. At analgesic doses, M6G causes similar reduction of the ventilatory response to CO_2 as an equianalgesic dose of morphine but significantly less depression of the hypoxic ventilatory response. Preliminary data indicate that M6G is associated less than morphine with nausea and vomiting, causing 50% and 75% less nausea in postoperative and experimental settings, respectively. Although the data from the literature are very promising, we believe that more studies are necessary before we may conclude that M6G is superior to morphine for postoperative analgesia.

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For more than 50 yr, morphine has been considered the most important drug for treatment of acute and chronic (malignant) pain, despite its many side effects, such as nausea/vomiting, sedation, constipation, and respiratory depression (1). The search for an equipotent analgesic with fewer side effects continues (2). Close examination of the natural metabolites of morphine in humans may have brought us such a compound. In humans, 60% of morphine is glucuronidated in the liver to morphine-3-glucuronide (M3G), whereas 6% to 10% is glucuronidated to morphine-6-glucuronide (M6G) (3). Although M3G lacks analgesic properties, animal data have shown that M6G is an analgesic acting at the μ-opioid receptor (4). Animal data examining the effects of M6G demonstrated as early as in 1950 that M6G is a more potent analgesic than morphine (5), whereas subsequent studies in animals and humans suggest that M6G has a more favorable side effect profile, causing less respiratory depression and nausea and vomiting than morphine (2,3). Evidently, a drug with equivalent analgesia to morphine but with intrinsically fewer side effects is of enormous advantage to the patient and may in the future replace morphine as the most important drug for treatment of severe pain.

In this short review we will discuss the compound M6G, its site of action, disposition and elimination, analgesic properties, and side effect profile to assess whether M6G indeed differs from morphine and whether it meets the criteria necessary to replace morphine as a postoperative analgesic.

Site of Action

M6G, like morphine, acts via the opioid receptor system as agonist at the μ-opioid receptor, the δ-opioid receptor, and the κ-opioid receptor (6). Relative to morphine, M6G has similar to 4 times less affinity for the μ-opioid receptor, similar affinity for the δ-opioid receptor, and 20 times less affinity for the κ-opioid receptor (6,7). Data from studies in mice that lack exon 2 of the μ-opioid receptor gene (*Oprm*) and consequently do not have functional μ-opioid receptors show that in these animals neither morphine nor M6G

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produces (spinal or supraspinal) antinociception or respiratory depression (8). This indicates that the *Oprm* gene mediates M6G and morphine's antinociceptive and respiratory effects, with little involvement of the δ-opioid receptor gene. However, one cannot exclude some developmental alterations in the δ-opioid system in this mouse strain as the result of the loss of μ-opioid receptor activity during development. Data suggest the existence of distinct μ-opioid receptors involved in morphine and M6G analgesia (9–11). Treatment of rats with antisense probes against exon 1 of the *Oprm1* gene significantly reduced morphine analgesia but failed to block M6G analgesia (9). Specific probes targeting specific G protein α subunits (μ-opioid receptors belong to the superfamiliy of seven-transmembrane domain receptors coupled to the G_i/G_o class of G proteins) indicate a distinct effect on morphine and M6G analgesia (10). Furthermore, exon 1 *Oprm* gene knockout mice show the persistence of M6G but not morphine analgesia (10). Although these data point towards the importance of exon 1 (the first transmembrane domain and the 5'extracellular terminal of the μ-opioid receptor), for morphine but not for M6G analgesia, this theory is not supported by other studies. For example, neither exon 1 nor exon 2 μ-opioid receptor gene knockout mice display G-protein activation (12). Furthermore, it has not been shown that M6G-specific analgesia (as observed in exon 1 μ-opioid receptor gene knockout mice (11)) is reversed with naloxone. Hence, the existence of a specific M6G receptor remains an issue of controversy.

In mice, Ling et al. (13) identified two subsets (probably splice variants) of the μ-opioid receptor, the μ_1-opioid receptor involved in the supraspinal analgesic effects of opioids and the μ_2-opioid receptor involved in opioid respiratory, gastro-intestinal and spinal analgesic effects. The receptor affinity profile of morphine and M6G differs for these two receptor subsets. M6G shows four times less affinity for μ_2-opioid receptor than morphine, with equal affinity at the μ_1-opioid receptor (14). These data support the hypothesis that M6G causes analgesia with less respiratory effect than morphine (see "Side Effect Profile" below).

Disposition and Elimination

In humans, little or no morphine or M3G is detectable in plasma after an IV M6G infusion, indicating the absence of significant metabolism of M6G (15). Some morphine (<1%) and M3G is produced in the gut and enterocytes after the elimination of M6G from the hepatocyte through the bile into the gut (enterohepatic cycle) (16). This latter process may account for the presence of minute quantities of morphine and M3G in plasma of humans given IV M6G (17). Using a three-compartment model we recently estimated the pharmacokinetic parameters after an M6G bolus dose of 0.3 mg/kg in a homogenous group of healthy volunteers (15). The volume of distribution, 0.20 L/kg, clearance, 1.9 $mL \cdot min^{-1} \cdot kg^{-1}$, and elimination half-life, 1.4 h, are in agreement with earlier findings (3,18). The variability among the subjects was small, with the coefficient of variation ranging from 11%–30%. In comparison with morphine, M6G's volume of distribution and clearance are smaller by a factor of about 10 (morphine's respective volume of distribution and clearance are 1.9 L/kg and 22.5 $mL \cdot min^{-1} \cdot kg^{-1}$), whereas its elimination half-life is of the same magnitude (2 h). The smaller volume of distribution of M6G as compared with morphine indicates that M6G distributes less well than morphine into tissues. This is probably related to the relative lesser lipophilicity of M6G relative to that of morphine.

It is generally assumed that the passage of M6G across the blood-brain barrier (BBB) is relatively slow when compared with morphine because of the hydrophilic nature of the M6G molecule (19,20). When we consider the blood-effect site equilibration half-life ($t_{1/2}k_{e0}$), human studies indicate that M6G equilibrates slowly with the postulated effect-site within the central nervous system. Based on data derived from analgesia and pupil diameter, M6G's $t_{1/2}k_{e0}$ ranges from 4 to 8 h (15,21). In comparison morphine's $t_{1/2}k_{e0}$ ranges from 1.6 to 4.8 h (21–23). There is growing evidence that the delay between morphine and M6G plasma concentration and measured effect is only partly related to its passage across the BBB. Studies in rats have shown that at least half of the delay is the result of drug distribution within the brain compartment, rate-limiting mechanisms at the receptor level, and neuronal dynamics (24,25). Furthermore, M6G's lipophilicity is of limited importance in crossing the BBB because in media of low polarity (such as the BBB) M6G molecules may fold and mask their polar groups (and thus increase their lipophilicity) and also may form Zwitterions (electronically neutral double ions pairs) (26).

Whether M6G is a substrate of active influx and efflux transporters across the BBB remains a matter of debate. In contrast to *in vitro* data (27,28), human and *in vivo* animal data do not support the idea that M6G is a substrate of the efflux transporter protein MDR1 P-glycoprotein P (PgP, a multidrug transporter belonging to the ATP-binding cassette (ABC) family of transmembrane transporters and essential component of the BBB) (29–31). There is evidence from animal studies that M6G is a substrate for the organic anion transporting polypeptide 2 (oatp2) and the glucose transporter GLUT-1 (32,33). These carrier systems are expressed at the luminal and abluminal sides of the brain endothelial cells and serve as influx and efflux transporters across the BBB. Recent animal data indicate that morphine glucuronides (M6G and M3G) are

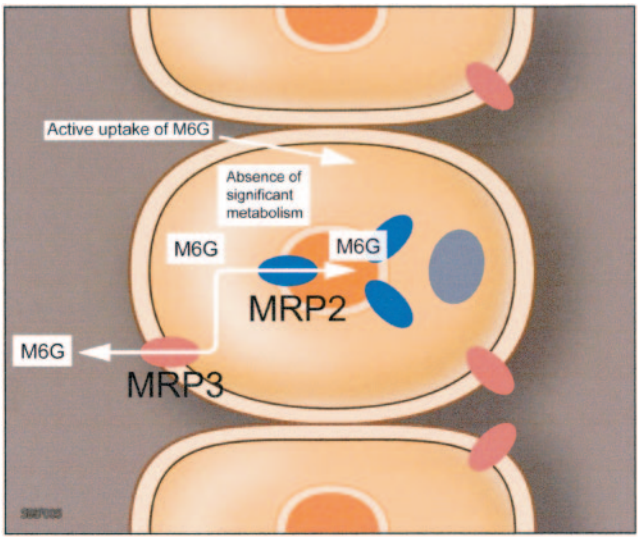

Figure 1. Transport of M6G in hepatocytes. Schematic representation of the fate of morphine-6-glucuronide (M6G) in the hepatocyte. M6G is actively pumped from the blood into the liver cell via a yet unknown transporter protein. M6G is not metabolized but is the substrate of efflux transporter proteins, multidrug resistance proteins Mrp3 and Mrp2. Mrp3 is expressed in the sinusoidal membrane of hepatocytes, transporting morphine glucuronides back into the bloodstream). Mrp2 is expressed in the cannicular membrane of hepatocytes, transporting M6G into the bile (cannicular sinuses: orange). In the gut M6G is deglucuronidated to morphine. Data adapted from (32).

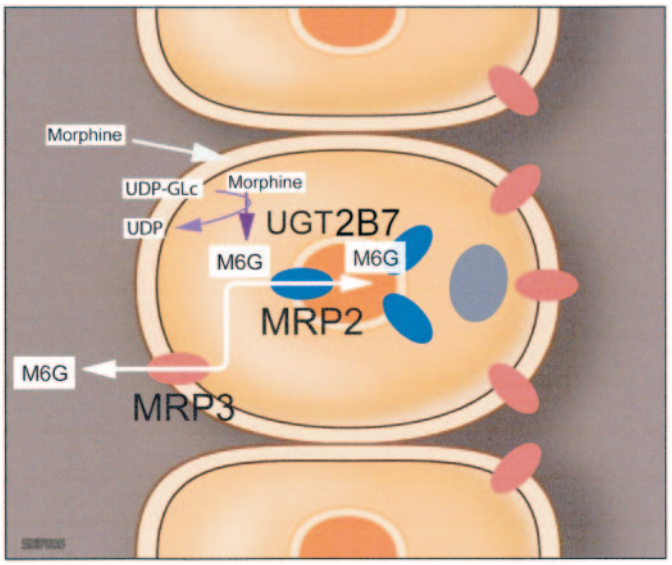

Figure 2. Metabolism and transport of morphine in hepatocytes. Schematic representation of the fate of morphine in the hepatocyte. Morphine is metabolized in the hepatocyte to morphine-3-glucuronide (M3G) (60%–70%) and M6G (5%–10%) in a reaction catalyzed by UDP glucuronosyl transferase 2B7 (UGT2B7). Both glucuronides are substrate of the efflux membrane proteins multidrug resistance proteins Mrp3 and Mrp2 (see Fig. 1).

substrates of the ABC transporter multidrug resistance proteins 2 and 3 (MRP2 and MRP3, Figs. 1 and 2) (34). However, in contrast to PgP (and oatp 2 and GLUT-1), MRP2 and MRP3 are not expressed in the BBB. MRP3 is present in the sinusoidal membrane of hepatocytes (transporting morphine glucuronides into the bloodstream) and the basolateral membrane of enterocytes (transporting morphine-glucuronides from the enterocyte into the bloodstream). MRP2 is present in the cannicular membrane of hepatocytes, where it transports M6G into the bile (34). Mice lacking the Mrp3 gene ($Mrp3^{-/-}$) are unable to excrete M6G from the liver into the bloodstream, resulting in the accumulation of M6G in the liver and bile and a reduction of M6G concentrations in plasma. Consequently the elimination of M6G is predominantly *via* feces in $Mrp3^{-/-}$ mice. In contrast, wild-type animals (as well as humans with normal renal function) eliminate M6G predominantly via the urine (>95%). Interestingly, the study in $Mrp3^{-/-}$ mice show evidence for an active uptake of morphine glucuronides from the blood into the hepatocyte via as yet unknown transporter proteins (possibly member(s) of the oatp carrier family) (34). In the gut M6G is deglucuronidated and the resultant morphine molecule is partly taken up by enterocytes (16). Enterocytes are able to glucuronidate morphine and transport the resultant glucuronide (M3G in mice, M3G and M6G in humans) to the bloodstream (note that, in contrast to humans, mice lack the ability to metabolize morphine to M6G) (16,34). As a consequence of the enterohepatic cycle, M3G is detected in the blood of wild-type mice injected with M6G but not in the blood of $Mrp3^{-/-}$ mice (see Fig. 5 in Zulcer et al. (34).

Distribution within the brain compartment differs for morphine and M6G (24,25,35). Whereas morphine accumulates predominantly intracellularly, M6G is found in the extracellular fluid. The difference in distribution may play a role in the difference in potency and onset/offset times for morphine and M6G. In contrast to M6G, morphine needs to diffuse from the intracellular to extracellular sites to activate the μ-opioid receptor.

Analgesic Properties of M6G

In laboratory animals, M6G causes effective and long-lasting antinociception and is more potent than morphine in various pain models (8,36–38). The potency ratio varies depending on the route of administration. In mice, we observed a potency ratio of 3:1 to 5:1 (M6G:morphine) after IP administration in heat pain assays (8). After central administration (intracerebroventricular or intrathecal) the potency ratio increases to values more than 300:1 (36,37).

Intrathecal M6G produces potent analgesia in perioperative and cancer patients (39,40). Studies using a peripheral route of M6G administration are more equivocal with respect to the analgesic properties of

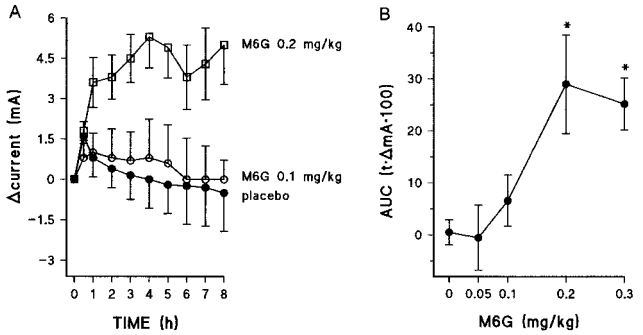

Figure 3. A, Effect of IV placebo (0.9% NaCl) and 0.1 and 0.2 mg/kg morphine-6-glucuronide (M6G) on the tolerance to electrical pain. A dose of 0.2 mg/kg, but not 0.1 mg/kg, is more effective than placebo in causing analgesia in a group of healthy female volunteers. B, Dose-response relationship of M6G on pain tolerance to electrical pain. On the *y*-axis, AUEC depicts the area-under-the time-effect (Δcurrent) curve. *$P < 0.05$ versus placebo. Data adapted from (15, 45).

M6G. Some studies that focused on "small-dose" single IV boluses (bolus dose ranging from 0.04 to 0.1 mg/kg) or short-term continuous IV infusions (dose in the first hour of administration <0.1 mg/kg) showed little or no analgesic effect (41,42), although others have reported an analgesic effect (43–46). We performed a dose-finding study (M6G dose range from 0.05 to 0.3 mg/kg) in a group of healthy young female volunteers and observed that 0.05 and 0.1 mg/kg did not produce analgesia responses greater than placebo (15,47). In contrast, doses of 0.2 and 0.3 mg/kg produced effective and long-lasting analgesia (Fig. 3) (47). These data indicate that the M6G dose-response curve is initially flat and shows a sharp rise at doses of 0.2 mg/kg or larger, in contrast to studies that found significant analgesia at M6G doses <0.2 mg/kg. The lack of placebo controls may especially explain some of the differences in outcome in some of the studies.

Recent clinical studies show that M6G is effective in the treatment of postoperative pain after orthopedic procedures. Dahan et al. (48) found that 0.4 mg/kg M6G produces long-lasting analgesia (>24 h) significantly longer than placebo in a multicenter study in 166 patients after knee replacement surgery. In a similar group of 66 and 100 patients, Hanna et al. (49) and Binning et al. (50) showed that M6G is as effective as morphine in producing analgesia using a patient-controlled system and IV bolus infusions, respectively. The dose at which M6G produces analgesia in efficacy equivalent to morphine has yet to be determined. Experimental and clinical studies indicate a M6G:morphine potency ratio (in terms of IV bolus dose) of 1:2 to 1:3 (15,49). In other words M6G 0.3–0.4 mg/kg produces equivalent analgesia as 0.15 mg/kg morphine. Using a pharmacokinetic-pharmacodynamic modeling approach (in volunteers) the M6G:morphine C_{50} ratio was found to vary from 1:5 to 1:10 (data derived from electrical pain and pupil diameter measurements; C_{50} = effect-site or steady-state plasma concentration causing 50% of effect) (15,22). This indicates that in terms of the steady-state M6G plasma concentration, a 5 to 10 times larger plasma concentration of M6G than of morphine is needed to reach a similar end-point, for example, a 50% increase in pain tolerance.

It has been suggested that M6G has (apart from a central mechanism of action) an important peripheral mechanism of analgesia (51). This could, at least partly, explain the effectiveness of M6G after orthopedic surgery (48–50). Peripheral opioid analgesia is clinically important, especially in arthritis and other inflammatory conditions (52). It has several advantages above a strictly central mechanism of analgesic action, such as lack of tolerance to opioid therapy (52) and reduced side effect profile.

Finally, despite the very small values of k_{eo} (long blood-effect site equilibration half-life) M6G's analgesia onset time is similar to that of morphine and well within 30 min after its IV administration (Fig. 3). This enables use of M6G in the direct postoperative period. However, we would encourage the IV infusion of M6G (or any other long-acting opioid such as morphine) at least 30 to 60 min before the end of surgery to ensure comfortable patient recovery after surgery.

Side Effect Profile

A drug that aspires to replace morphine as the most prominent analgesic for treatment of acute pain, needs to have a more favorable side effect profile (apart from the need for similar analgesic efficacy and cost effectiveness). We will discuss two side effects which have an important impact on postoperative practice: nausea/vomiting and respiratory depression. Postoperative nausea and vomiting (PONV) causes severe discomfort to the patient and its presence or absence is directly related to the level of patient satisfaction. Severe respiratory depression is potentially life-threatening.

Nausea and Vomiting

In 4 studies in which 104 volunteers received a single IV infusion of M6G in doses ranging from 0.05 to 0.6 mg/kg, we observed that just 15 subjects (all women) became nauseated (<15%) and none vomited (15,51–53). Indeed, most subjects received a light lunch during the studies without consequences, suggesting the absence of significant changes in gastrointestinal motility after M6G administration. These data contrast sharply with our studies on other opioid compounds, such as morphine, buprenorphine, and fentanyl, which were associated with nausea in 45% to 90% and vomiting in 30% to 45% of volunteers (22,56).

The picture is different, however, after a long-term M6G infusion. In one study in healthy volunteers using a bolus and continuous infusion of M6G there was no difference in the frequency of nausea between the two treatment groups (data in volunteers) (17). In agreement with our observations in volunteers using single infusions, clinical studies suggest that the occurrence of PONV is less with IV M6G compared with IV morphine (48,50,57). PONV occurred twice as often after morphine than after M6G at various postoperative time points. However, none of these clinical studies was designed to study PONV as the primary endpoint. Hence, we would like to stress the need for clinical studies on the comparison of occurrence of PONV (severity and frequency) after M6G administration and other commonly used postoperative analgesics. Assuming a 50% reduced rate of PONV with M6G the study size does not need to be excessive.

Respiratory Depression

Animal data indicate greater M6G potency in causing respiratory depression relative to morphine. Ratios vary from 1:4 (IP administration) to 1:10 (intracerebroventricular) depending on the method of opioid infusion (8,36,58–60). In mice, we observed that IP M6G was four times more potent than IP morphine in causing depression of the hypercapnic ventilatory response (HCVR) slope (8). Similarly, in this same mouse strain, M6G displayed a fourfold greater antinociceptive potency than morphine. These data indicate that at equianalgesia, morphine and M6G produce equipotent respiratory effects. In humans, there have been few studies concerning the influence of M6G versus morphine on breathing (44,46,61). The results of the majority of these studies suggest either a reduced respiratory effect of M6G in comparison to morphine, no effect of M6G on respiration, or a small stimulatory effect by M6G. These results are difficult to interpret because 1) often very small doses of M6G were tested (<0.1 mg/kg); 2) the doses of M6G and morphine tested were not equipotent with respect to analgesia; 3) respiratory effects were not related to plasma opioid concentrations; 4) studies were not placebo controlled; 5) actual arterial or end-expiratory concentrations of carbon dioxide are not reported during CO_2 inhalation. We assessed the effect of IV M6G (0.2 mg/kg) and morphine (0.13 mg/kg) in a placebo-controlled double-blind study using the computer controlled "dynamic end-tidal forcing technique" (53). We observed that, at equianalgesic doses, the effects of morphine and M6G on the HCVR were comparable (Fig. 4), both with respect to the magnitude of depression of the response slope and to the time profile. In contrast, the effects of morphine and M6G on ventilatory response to isocapnic hypoxia did differ significantly, with little or no depression of this important

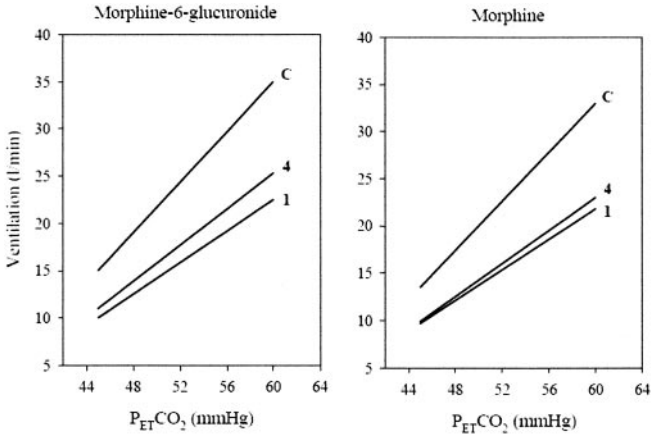

Figure 4. Effect of 0.2 mg/kg IV morphine-6-glucuronide (left) and 0.13 mg/kg IV morphine (right) on the ventilatory response to carbon dioxide in a group of healthy volunteers. C is the population response before any drug was given (control response); 1 and 4 are the population responses 1 h and 4 h after drug infusion. The effect of both drugs with respect to magnitude of respiratory depression and time course of effect were similar over the 4-h time span. Data adapted from (51).

reflex response by M6G, but with severe and long-lasting depression by morphine (Fig. 5). In terms of dose, two times larger doses of M6G were needed to suppress the HCVR, whereas five times larger doses were needed to suppress the ventilatory response to hypoxia. In two subsequent studies, we were able to confirm these observations using a pharmacokinetic-pharmacodynamic approach (54,62): C_{50} values for analgesia and depression of the hypoxic ventilatory response were similar for morphine but differed by approximately 40% for M6G (with larger C_{50} values for hypoxic respiratory depression). The differences in the effect of M6G, but not morphine, on hypoxic and hypercapnic breathing are remarkable and may be explained by 1) differences in morphine and M6G distribution within the brain compartment; 2) the existence of distinct receptor/G-protein complexes for morphine and M6G, with limited expression of the M6G-specific complexes in neuronal pathways involved in sensing and processing of the ventilatory response to hypoxia; 3) the development of acute tolerance to M6G, but not morphine, in hypoxic signaling pathways. Further studies are required (at analgesic equipotency) to further explore the respiratory behavior of morphine and M6G, especially in postoperative patients, and to assess whether the observed differences in M6G's effect on hypercapnic and hypoxic breathing is not related to a type II statistical error (i.e., the under-estimation of M6G's effect on the ventilatory response to hypoxia).

Accumulation of M6G in Renal Failure

Because M6G is eliminated from the body predominantly via the kidney, it will accumulate in patients

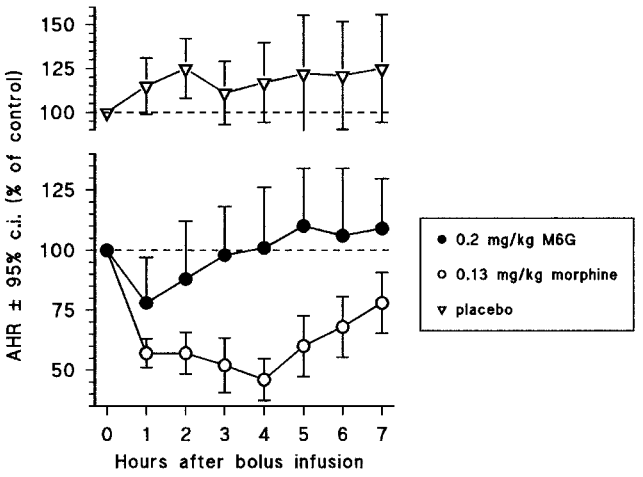

Figure 5. Effect of 0.2 mg/kg IV morphine-6-glucuronide (M6G), 0.13 mg/kg IV morphine, and placebo on the ventilatory response to isocapnic hypoxia in a group of healthy volunteers. M6G causes short-term depression of the ventilatory response to hypoxia. Significant depression occurred at time t = 1 after M6G infusion. Morphine causes long-term depression of the ventilatory response to hypoxia. Significant depression occurred from time t = 1 h after morphine infusion lasting beyond t = 7 h. Values are mean ± 95% confidence interval. Data adapted from (51).

with renal failure (15). In simulation studies it was shown that in patients with no renal clearance, brain M6G concentrations will increase by a factor of 10 after repeated IV dosing compared with normal patients (15). This will result in the increased probability of opioid-related side effects. Lötsch et al. (63) collected 9 case studies in which renal failure patients developed various side effects after large-dose morphine administration [Table 1 in Lötsch et al. (63); also note references cited therein]. These side effects, ranging from nausea to sedation and respiratory depression, were best explained by M6G accumulation. These observations indicate the need for caution in the use of M6G in patients with renal impairment. Further studies on M6G's pharmacokinetics and pharmacodynamics in this patient group are needed to fully understand M6G's behavior in these patients and to answer questions such as: "will hepatic elimination of M6G increase in renal failure patients?" and "what dosing scheme should be adopted to prevent side effects?"

Gender and Pharmacogenetics

Physicians using analgesics for the treatment of acute and chronic pain are aware of the large interpatient variability in intended and adverse effects. An increasing number of studies have shown the importance of gender in explaining part of this variability. For example, both experimental and clinical studies show a gender difference in morphine's analgesic properties—which are related to gender differences in morphine's pharmacodynamics but not pharmacokinetics—with greater morphine potency but slower onset/offset times in women than men (22,64). Clinically this is reflected by the increased need for morphine postoperatively (as a result of the slow morphine onset) and a reduced opioid consumption in the 24 to 48 h postoperative period in females compared with males. For M6G, no such gender differences were detected: both pharmacokinetics and pharmacodynamics were similar in men and women (15).

Apart from gender, other genetic mechanisms may also underlie the marked variability observed in opioid effect. As previously discussed, morphine and M6G produce their intended and adverse effects by an action at the MOP receptor. Studies have identified several single nucleotide polymorphisms (SNPs) of the μ-opioid receptor gene. In humans, the gene, *OPRM1*, is located on chromosome 6q24-q25 (65). These SNPs become clinically relevant when they are abundant within the population and the resultant alteration in the amino acid sequence of the gene product (i.e., the μ-opioid receptor) is associated with changes in phenotype (i.e., opioid efficacy). The most widespread SNP of the μ-opioid receptor gene associated with a change in the amino acid sequence and causing changes in phenotype is the substitution of the nucleotide adenine (A) with guanine (G) in exon 1 at nucleotide position 118 (in the official nomenclature of the Human Genome Variation Society *OPRM1: c.118A>G*; frequency of the mutated allele is 10%–30% in the Caucasian population). The result of this substitution is the exchange of amino acid asparagine (Asn) by aspartate (Asp) at amino acid position 40. Various studies have shown that the 118A>G SNP causes a reduction in opioid potency and efficacy. For example, cancer patients, homozygous for the 118G allele, require twice as much morphine to achieve adequate pain relief compared with patients homozygous for the 118A allele (66). Also M6G's effect is attenuated in persons with at least one 118 G allele, exhibiting a 2 to 3 times reduction in analgesic potency and an ability to constrict the pupil (15,17,52,67). The effect of the 118A>G mutation on morphine and M6G's side effect profile remain unclear. One study (in 16 subjects, of which 4 subjects were heterozygous carriers of the variant *OPRM1* allele) showed that the *OPRM1:c.118A>G* mutation is not associated with a decrease in M6G's potency for respiratory depression (54). In postoperative patients, the implications of being a carrier of the 118A>G mutation would then be the need for larger morphine and M6G doses for adequate pain relief, with a greater chance of respiratory depression. In a case study of one 118A>G patient with renal failure, a reduced morphine side-effect profile was observed despite large plasma concentrations

of M6G (>1700 nM, *cf.* C_{50} for respiratory depression 1000 nM) (63). Note that although the evidence of reduced morphine and M6G analgesic efficacy in carriers of the 118A>G mutation is moderate to strong with evidence across multiple pain models, further studies are needed to verify the effect the 118A>G mutation has on the side effects these opioids invariably produce. Also, SNPs in other genes, such as the melanocortin 1 receptor gene, are associated with changes (increases) in morphine and M6G analgesic potency (55). Their effect on opioid side effects has not been examined.

Conclusions

Morphine and M6G exhibit their intended and adverse effects via the μ-opioid receptor. Evidence for the existence of a special M6G μ-opioid receptor variant is weak and requires further study and confirmation. In contrast to morphine, M6G causes long-term pain relief in humans, although its analgesic potency is less than that of morphine. As a result of this decreased potency, two to three times the IV morphine dose is required to reduce acute pain in postoperative patients to acceptable levels (visual analog scale <3 cm). At these doses pain relief lasts for periods >24 h. That M6G is associated with fewer side effects (in frequency and severity) than morphine at equianalgesic doses may be concluded from several studies showing less nausea and vomiting and less respiratory depression (that is, depression of the ventilatory response to hypoxia rather than the HCVR). However, the number and sample size of investigations specifically aimed at studying the full spectrum of M6G's effect (intended effects and adverse effects) are limited. Because M6G's place as the successor of morphine is predominantly determined by the more favorable side effect profile compared with that of morphine, we believe that more evidence is necessary and, consequently, more studies are required. Only when these studies show that the occurrence of specific side effects such as PONV and respiratory depression are reduced by 50% or more with M6G compared with morphine, whereas pain relief is adequate and comparable to that after morphine administration, M6G may be considered a true and superior successor of morphine.

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