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Role of Morphine's Metabolites in Analgesia: Concepts and Controversies

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ABSTRACT

The metabolites of morphine, morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G), have been extensively studied for their contribution to clinical effects following administration of morphine. Those contributions to both the desired effect (ie, analgesia) and the undesired effects (eg, nausea, respiratory depression) are the subject of clinical controversy. Much attention and effort have been directed at investigating the properties of M6G because of interest in this substance as a possible substitute for morphine. It exhibits increased potency and the possibility of a better side effect profile compared with morphine, although the reported relative benefits vary widely. M3G is not analgesic, but its role in producing side effects, including the development of clinical tolerance, has been proposed. This review is focused on M6G and the factors that contribute to its clinical utility. The formation and distribution of M6G are presented, as are the analgesic effect and the onset of this effect. The impact of genetics, age, and gender on M6G and its effects is also reviewed.

KEYWORDS: Morphine, morphine-6-glucuronide, clinical pharmacology, clinical covariates

INTRODUCTION

Morphine, the prototypical opioid analgesic, is metabolized in vivo primarily to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). These metabolic products account for ~65% of a dose of morphine, with the remaining drug biotransformed to multiple minor species or excreted unchanged.[1] These primary metabolites have been the focus of extensive basic and clinical evaluation for more than 25 years as investigators seek to better understand factors that contribute to opioids' analgesic effect and side effects. We have also been addressing issues related to the impact these metabolites may play on differences between patients who receive a standard dose of morphine.[2] While much is still unknown about the clinical pharmacology of morphine metabolites, what emerges from this body of literature is an understanding of the physicochemical and pharmacologic differences between the metabolites and the parent drug that explain their unique pharmacology and provide insight into both genetic and demographic differences (eg, gender, age) that exist for these therapeutic compounds.

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ENDOGENOUS METABOLITE FORMATION

Morphine is primarily metabolized in the liver by urldine-5′-diphosphate (UDP) glucuronosyltransferase, with specific affinity for the UGT2B7 isozyme. This isozyme is responsible for the formation of both glucuronide species. The differential amounts of metabolite formation (5 times more M3G is formed than M6G) have lead researchers to postulate that there is another metabolic isozyme that primarily forms M3G. Although in vitro results have indicated a possible role of UGT1A1 in the formation of M3G, in vivo the 2B7 isozyme is the primary morphine metabolite location.[3] The difference in formation of these 2 metabolites is more likely due to physicochemical and steric issues that affect the binding of morphine to the phase II enzyme.[1]

UGT2B7 is the primary enzyme for morphine metabolism, but it is also responsible for the metabolism of several endogenous and exogenous compounds. Chief among them are the steroid hormones, and also bilirubin in newborn infants. While these compounds are substrates for UGT2B7, they are also metabolized by other liver enzymes. Thus, these compounds could interfere with the production of morphine metabolites in vivo. Several substances can also serve in this capacity, including ranitidine, naltrexone, naloxone, and ethanol.[1,4,5]

Repeated injections of heroin in rats were shown to increase plasma levels of M6G (which were undetectable in the rats that received morphine instead of heroin) and to decrease the plasma levels of M3G. After the heroin injections were discontinued, the metabolism of morphine returned to

normal.[6] This phenomenon was also seen in humans. Long-term intravenous heroin abusers given morphine or street heroin made more M6G and less M3G than nonheroin users given morphine.[7] Although heroine is a prodrug for morphine, the rationale for the influence of heroin on M6G formation is not known.

Analgesic Onset of Effect

In terms of pharmacological activity, M6G is an opioid agonist with a potency that is 2 to 4 times greater than morphine's, although these values vary widely depending on the study design used to assess drug effect. While relative potency in animals has been reported to range from 1:1 to 678:1, the range in humans is consistently reported to be in this lower range of 2 to 4:1.[8] In contrast, M3G is inactive and is reported to have little pharmacologic activity, although its role in contributing to analgesic effect and side effects is disputed.[9-14]

This increased potency of the M6G metabolite relative to morphine has been postulated to be related to the ability of M6G to exist at higher concentrations at the receptor sites in the central nervous system (CNS), rather than reflecting a significant difference in pharmacologic potency.[15] M6G is significantly less lipophilic than morphine, which substantially reduces its relative blood-brain barrier permeability. Yet its CNS uptake rate is greater than would be predicted based on the reduced level of lipophilicity and permeability. This suggests that M6G may be taken up into the CNS by an active transport mechanism.[16]

M6G crosses the blood-brain barrier slowly, showing a maximum concentration in the range of 6 hours for human volunteers after an intravenous dose.[17] The analgesic effect from M6G persists for a longer period of time than suggested by its elimination from the plasma. This is due to a significantly prolonged CNS clearance compared with systemic levels.[18] The effect may be prolonged in patients with renal failure because of metabolite buildup even though the metabolite is cleared from the blood during hemodialysis.

Experimental evidence from rats regarding factors that influence the effect of M6G on analgesia found that the delay in CNS effect was due to transport across the blood-brain barrier and also to distribution in the brain tissue or rate-limiting mechanisms at the receptor level.[19] In situ experiments using mouse brain found that M6G is not transported by P-glycoprotein or multidrug resistance protein 1 but is transported by GLUT-1 and a digoxin-sensitive transporter. These transporters are found on the luminal and abluminal sides of the brain endothelial cells, which may allow for bidirectional transport of M6G.[20] Although the previous study did not show that M6G was transported by P-glycoprotein, it has been shown that when the P-glycoprotein inhibitor PSC833 was given to rats receiving M6G, spinal cord tissue concentrations of M6G and antinociceptive effects were increased,[21] which was probably (as with probenecid) a secondary consequence of reduced systemic clearance rather than altered transport across the blood-brain barrier.[18]

Analgesic Activity

Experimental evidence from volunteer studies has shown that when M6G is administered intravenously, it has significant analgesic activity.[22] This result is in contrast to results from a study comparing morphine sulfate to M6G in patients undergoing major joint replacement surgery; it was found that patients receiving M6G had higher pain scores at 30 minutes and 1 hour postsurgery.[23] Furthermore, in a study comparing a single dose of morphine to a single dose of M6G at the end of open knee surgery, it was found that the placebo group and the M6G group required greater amounts of morphine from a patient-controlled analgesia pump than did the group that received the dose of morphine.[24] These conflicting reports exist for both clinical trials and volunteer experiments. While these differences are not fully understood, it appears that when M6G is directly administered intravenously in patients, the concentrations that produce acute analgesia are an order of magnitude higher than the concentrations that result from its metabolism from morphine.[8] Given M6G's relatively long time to peak effect, large doses of M6G may be needed to produce adequate concentrations in the CNS for acute analgesia. The conflicting reports on its efficacy after intravenous administration may indicate that too small a dose was administered or too short a time was allowed for assessment of its effect.[8] When M6G is given intrathecally, it produces profound analgesia in both animal and human clinical studies.[25,26] This further supports the idea that factors that affect the ability of M6G to cross the blood-brain barrier after direct intravenous administration may contribute to reported differences in its analgesic effect.

In addition to the liver, human brain homogenates have been shown to metabolize morphine at nanomolar concentrations to M3G and M6G, supporting the idea that M6G in the CNS may be formed there directly from morphine, which penetrates the blood-brain barrier at a greater rate than M6G.[27] Interestingly, this study also found a concentration dependency in the M3G/M6G ratio formed by the brain homogenate. At lower concentrations of morphine, the M3G/M6G ratio was lower, perhaps indicating a preference for forming M6G when less morphine is present.[27] These factors add to the complexity of understanding the relative contribution of M6G to analgesia when it is formed from morphine and comparing it with M6G's direct administration as an analgesic agent. It is clear that M6G has a very different absorption, distribution, metabolism,

and excretion profile from morphine both systemically and at the site of drug effect; these differences contribute to the complexity of understanding the clinical pharmacology of this analgesic.

Further work is required to examine the clinical pharmacology profile of M6G. There is evidence that M6G reduces the severity of respiratory depression and nausea compared with morphine.[26,28,29] Whether M6G penetrates differentially to areas of the brain involved in pain, nausea, vomiting, and respiratory control or whether various opioid receptors in these brain areas differ in their pharmacology remains to be determined.[15,30] For instance, it has been shown that M6G has greater affinity for the μ_1 receptor subtype than for μ_2, the latter of which is thought to contribute to the negative side effects caused by opioids.[8] Furthermore, the opioid receptor is coded by a single gene that has at least several exons.[31] Knockout studies have shown that M6G and morphine have different sensitivities when alterations at exons 1 through 3 are evaluated.[32,33] These authors postulate the presence of a distinct receptor for M6G that may be important in the regulation of endogenous opioids, a premise supported by other groups as well.[16]

Genetics

Studies that relate differences in the genes that code for the enzyme for metabolizing morphine to M6G and for the mu opioid receptor have been conducted to determine whether these factors may contribute to the differential pharmacology of morphine and M6G. An extensive review of this literature was recently published by Lotsch et al.[21] With regard to morphine metabolism and M6G formation, the primary results have shown that morphine glucuronidation is unaffected by numerous UGT2B7 mutations, including the UGT2B7 H268Y polymorphism.[21] Interethnic differences have been seen between Caucasians and Native Americans, with the latter forming less M6G for an equivalent dose.[21] Multidrug resistance protein 3 (MRP3) polymorphisms may account for differences between individuals in M3G and M6G levels. MRP3 is the only transporter of M3G out of liver cells into plasma. In its absence, M3G is excreted in the bile in rats.[34]

Variants in the gene that codes for the mu opioid receptor have been linked to clinically measurable differences in the opioid effect of M6G. In particular, M6G was shown to have decreased efficacy with the A118G allele of the OPRM1 gene in homozygous carriers of the mutation when compared with the wild-type allele.[35] The same group found a decreased potency of M6G in both heterozygous and homozygous A118G carriers, with a larger decrease seen in the homozygous carrier.[36] Another group found that while the analgesic efficacy of M6G is reduced in those carriers of this mutation, it does not protect against respiratory effects.[37]

A fascinating observation shown to occur in both mice and red-haired humans was that a mutation resulting in loss of function at the melanocortin 1 receptor gene was associated with greater analgesia from M6G.[38] This finding was gender independent, which contrasts with previous findings related to this mutation that showed a greater impact in women compared with men for predominantly the κ−opioid agonist pentazocine. These results indicate that differences in effect for a given dose of morphine may be related to both pharmacokinetic and pharmacodynamic phenotypes; these factors need to be independently assessed to better understand the role of M6G in the level of analgesia produced by morphine.

Impact of Gender and Age

Both gender and age contribute to differences in the pharmacokinetics of M6G and morphine that will ultimately affect pharmacologic effect. Results from our group showed that elderly women had higher levels of morphine metabolites compared with elderly men and that their clearance of the metabolites was reduced.[2] Further analysis revealed that progesterone levels may affect the clearance rates for the M3G metabolite in particular, which could contribute to its accumulation in elderly women who are on chronic opioid therapy.[39] Since the metabolites of morphine are cleared renally, it is anticipated that decreased renal function with age would also result in lower systemic clearance of both metabolite species, leading to longer accumulation of M6G and potentially extended effect.

Murthy et al constructed a model to investigate the contribution of M6G to morphine analgesia in humans.[40] Their study included 8 volunteers, 3 males and 5 females, and found that M6G contribution was extremely variable, ranging from <0.1% to 66%. They also found a gender difference in the contribution of M6G to analgesia, with the average contribution in males being 32% and in females 13%. The M6G contribution was inversely related to the overall effect elicited by the morphine dose.[40]

Conclusions

M6G is formed endogenously from the metabolism of morphine by the UGT2B7 isozyme. While M6G has a greater analgesic effect than morphine when administered intrathecally, the effects of exogenous M6G when administered intravenously are complex. The passage of M6G across the blood-brain barrier is slow and appears to be one of the primary factors in the difference in analgesic effect between systemic morphine and M6G. Additionally, evidence suggests that morphine is metabolized to M6G in the brain, which further complicates the evaluation of M6G as an analgesic compared with morphine.

The differences between the side effect profiles of M6G and morphine are encouraging for the potential therapeutic use of M6G, but they need further confirmation. These differences may be due to different effects at the same receptor or actions of M6G at a distinct receptor. M6G's effect has been shown to be influenced by variants in the gene that codes for the mu opioid receptor, particularly in the A118G allele of the OPRM1 gene. The presence of this allele is associated with decreased efficacy. Gender and age are both important factors in the analgesic effect of morphine and M6G. Continued investigation is necessary to resolve the controversies surrounding M6G and to further our understanding of its actions and interactions in the body.

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