Review Article

Relationships Among Morphine Metabolism, Pain and Side Effects During Long-Term Treatment: An Update

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Abstract
The two metabolites of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), have been studied intensively in animals and humans during the past 30 years in order to elucidate their precise action and possible contribution to the desired effects and side effects seen after morphine administration. M3G and M6G are formed by morphine glucuronidation, mainly in the liver, and are excreted by the kidneys. The metabolites are found in the cerebrospinal fluid after single as well as multiple doses of morphine. M6G binds to opioid receptors, and animal studies have demonstrated that M6G may be a more potent analgesic than morphine. Results from human studies regarding the analgesic effect of M6G are not unanimous. The potency ratio between systemic M6G and morphine in humans has not been settled, but is probably lower than previously assumed. Hitherto, only a few studies have found evidence for a contributory effect of M6G to the overall effects observed after morphine administration. Several studies have demonstrated that administration of M6G is accompanied by fewer and a milder degree of opioid-like side effects than observed after morphine administration, but most of the studies have used lower doses of M6G than of morphine. M3G displays very low affinity for opioid receptors and has no analgesic activity. Animal studies have shown that M3G may antagonize the analgesic effect of morphine and M6G, but no human studies have demonstrated this. M3G has also been connected to certain neurotoxic symptoms, such as hyperalgesia, allodynia and myoclonus, which have been observed after administration of M3G or high doses of morphine in animals. The symptoms have been reported sporadically in humans treated primarily with high doses of morphine, but the role of M3G in eliciting the symptoms is not fully elucidated.

Introduction
Opium has been known and used as an analgesic since ancient times. It consists of the dried juice obtained from the unripe seed capsules of the opium poppy, Papaver Somniferum. Opium contains several alkaloids, of which
only a few—morphine, codeine, noscapine, and papaverine—have clinical usefulness.\textsuperscript{1} Friedrich Sertürner, a German pharmacist, isolated the component of opium with the most marked analgesic activity in 1806 and named it morphium after the god of dream in Greek mythology, Morpheus. It was later renamed morphine after a suggestion from the French chemist and physicist Gay-Lussac.

Although several new synthetic strong opioids have emerged in the past century, morphine is still the most widely used opioid throughout the world. Due to a more liberal approach to opioid analgesics, especially in cancer patients and, more recently, also in patients with pain of chronic nonmalignant origin, the consumption of opioids is increasing. As morphine is no longer only used for short-term pain relief, as in postoperative pain states and during the last hours of a dying patient, new problems and questions regarding its effect and mode of action during long-term use have arisen.

\textbf{Chemistry of Morphine}

Morphine is a phenanthrene alkaloid and consists of five condensed rings (Figure 1). The C3 phenolic and the C6 secondary alcoholic group, together with the amino group, make the otherwise structurally rigid morphine molecule chemically active. Morphine is a weak base with a pK\textsubscript{a} of 7.9; at physiological pH, 76\% of the molecules are ionized. Because of the two hydrophilic \(-\text{OH}\) groups present at the C3 and C6, morphine is relatively water-soluble and poorly lipid-soluble.

\textbf{Analysis of Morphine and its Glucuronidated Metabolites}

There are two main methods that have been used routinely for determining the contents of morphine and its glucuronides in body fluids: radioimmunoassay (RIA) and chromatography. A disadvantage of the RIA method is the lack of specificity between morphine and its glucuronides. Recently, chromatography in the form of high-pressure liquid chromatography (HPLC) has become the most widely used method, as it makes it possible to separate morphine and its metabolites.

\textbf{Mechanism of Morphine Action}

Consequences of morphine administration may include the wanted effect of antinociception and the unwanted side effects of respiratory depression, miosis, euphoria, sedation, reduced gastrointestinal motility, nausea and vomiting, alterations of the endocrine and autonomic nervous system, pruritus, and flushing of the skin.\textsuperscript{1} Morphine and other opioids exert their analgesic action by a specific interaction with one or more subclasses of the three most important opioid receptors related to antinociceptive control, which are designated as mu, delta, and kappa. Morphine is a pure opioid agonist with affinity primarily to the mu receptor and, to a lesser degree, to the kappa and delta receptors.

\textbf{Morphine Pharmacokinetics}

\textbf{Absorption}

After oral administration, morphine is almost completely absorbed from the gastrointestinal tract.\textsuperscript{2,3} Studies in the rat have showed that the most rapid absorption of morphine takes place in the alkaline medium of jejunum and duodenum, where morphine is mainly unionized. In the acid environment of the stomach, morphine is for the most part ionized and absorption is consequently poor.\textsuperscript{4}

\textbf{Elimination}

\textbf{Morphine Metabolism.} Only a minor fraction of the morphine absorbed after oral administration reaches the systemic circulation. Due to extensive first pass metabolism, bioavailability is low and variable. Mean values have reported to vary between 19\% and 47\%.\textsuperscript{3,5–8}

The two quantitatively and qualitatively most important morphine metabolites are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Only small amounts of
morphine-3,6-diglucuronide, morphine-3-ethereal sulfate, normorphine, and normorphine-6-glucuronide are produced (Figure 2). The formation of codeine from morphine is controversial.\(^9\) Regardless of the mode of administration, approximately 44–55% of a morphine dose is converted to M3G, 9–10% to M6G, and 8–10% is excreted in the urine unchanged.\(^8,12\) Four percent of a morphine dose is excreted as normorphine and its glucuronide metabolites.\(^13\) The remaining part may be explained by excretion via other routes (e.g., feces and perspiration) and through formation of minor metabolites, such as morphine-3,6-diglucuronide and morphine-3-ethereal sulfate.\(^14\)

The major pathway for morphine metabolism is conjugation with the co-substrate uridine diphosphate (UDP) glucuronic acid. The process is catalyzed by a UDP glucuronyltransferase (UDPGT). Depending on whether this process takes place at the 3 or 6 carbon position, M3G or M6G is formed.

\[
\text{UDP glucuronyltransferase} \\
\downarrow \\
\text{Substrate} + \text{UDP-GA} \rightarrow \text{Substrate-glucuronide} + \text{UDP}\]

Metabolism predominantly takes place in the liver,\(^16\) but in vitro studies have also demonstrated UDPGT activity in the kidney,\(^17\) gut,\(^18,19\) and brain.\(^20,21\) It has been indicated that two different isoforms of UDPGT are involved in the glucuronidation process in humans.\(^22,23\) However, a recent study has demonstrated that the human UGT2B7 is likely to be the major isoform responsible for morphine glucuronidation in humans, capable of catalyzing the glucuronidation process at both the 3- and 6- positions in ratios similar to the ratio of the two glucuronides found in human urine.\(^24\)

The clinical importance of the UDPGT activity found in organs other than the liver is not settled. In several studies, systemic clearance values of morphine exceeding hepatic blood flow have been observed.\(^25,26\) In a study of patients with normal liver function, it was found that 38% of the clearance of morphine was attributable to an organ other than the liver, probably the kidney.\(^26\) In cirrhotic patients the percentage of systemic clearance of morphine unaccounted for by the hepatic clearance was greater (33%) than in the controls (10%),\(^25\) which could lead to speculation of increased compensatory glucuronidation by extrahepatic organs in the case of hepatic impairment. In vitro studies have demonstrated UDPGT activity in the intestine,\(^18,19\) but a clinical study was not been able to confirm any glucuronidation activity at this location.\(^26\) This may imply that in case of normal function of the liver, the intestinal glucuronidation activity may be negligible.

In the human brain, formation of M3G and M6G has been observed in the microsomal fraction of brain tissue,\(^20\) and the presence of human UGT2B7 has also been demonstrated in the human nervous system.\(^21\) Two clinical studies with intracerebroventricular (ICV) administration of morphine have indicated that the human brain is able to metabolize morphine to M3G\(^27,28\) and M6G in vivo,\(^28\) as morphine and the metabolites were present in cerebrospinal fluid (CSF) while being undetectable in plasma.

**Ratios of M3G and M6G to Morphine.** Studies in patients receiving long-term treatment with morphine have demonstrated mean molar plasma M6G: morphine ratios of the order of 3.4–9 and mean molar plasma M3G:morphine ratios between 22 and 56 (Table 1). A single study found mean M6G:morphine and M3G: morphine ratios as high as 17 and 109 respectively.\(^29\) Mean or median M3G:M6G plasma ratios in cancer patients receiving long-term morphine treatment have been found to vary between 5.8 and 9.0 (Table 1). Urinary metabolite:morphine ratios have been found to be higher after oral than parenteral administration, which probably is caused by the first-pass glucuronidation through the liver.\(^30\)
Excretion of Morphine and its Metabolites. The prominent role of the kidney in the excretion process of morphine metabolites has been demonstrated in a study of patients with renal failure given intravenous (IV) morphine. Subsequent plasma concentrations of M3G and M6G were observed to be several-fold greater in these patients than in a control group with normal renal function. When kidney transplantation was performed in the patients with renal impairment, the metabolite accumulation was abolished.31

Consequences of Hepatic Dysfunction. As the liver is the most important site for the glucuronidation of morphine, it might be expected that impairment of the liver function would produce alterations in morphine metabolism. One of the first studies in this area found that patients with stable cirrhosis did not exhibit impaired disposition and elimination of morphine.32 In contrast, a later study found that when comparing a group of cirrhotic patients with a control group, the hepatic plasma flows were virtually identical, but there was a 25% reduction in morphine hepatic extraction ratio in the cirrhotic patients compared to the controls. The authors concluded that the impairment of morphine metabolism was due to a reduction in intrinsic hepatic clearance.25 Other studies in patients with non-malignant chronic liver disease have found a reduced metabolite production, reduced morphine clearance and a prolonged terminal half-life of morphine after morphine administration.33,34 Differences in the severity of the liver disease may at least partly account for the discrepancies of some of the data reported.35 Data suggest that, in severe liver disease, glucuronidation may be impaired, but in milder disease, this metabolic pathway may be preserved. Extrahepatic metabolism of morphine may play a significant role in patients with impaired liver function.25,26

Consequences of Renal Impairment. The influence of renal function on the excretion of morphine has been discussed. In two older works, the renal excretion of morphine was not found

### Table 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects (n)</th>
<th>Kidney (K) and liver (L) Function</th>
<th>Oral Morphine Formulation</th>
<th>Route of Administration</th>
<th>Sampling (Time of Sampling)</th>
<th>M3G/M Mean Values (range)</th>
<th>M6G/M Mean Values (range)</th>
<th>M3G/M6G Mean Values (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>68 Cancer patients (10)</td>
<td>K: Not Stated, L: Not stated</td>
<td>MS</td>
<td>Oral</td>
<td>Several</td>
<td>56</td>
<td>9</td>
<td>Not calculated</td>
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<tr>
<td>97 Cancer patients (59)</td>
<td>K: Mixed, L: Not stated</td>
<td>MS (n=24)</td>
<td>Oral</td>
<td>Single sample (through)</td>
<td>34.5 (MS)</td>
<td>5.8</td>
<td>Not calculated</td>
<td></td>
</tr>
<tr>
<td>29 Cancer patients (34)</td>
<td>K: Mixed, L: Not stated</td>
<td>SR morphine</td>
<td>Oral</td>
<td>Single sample (through)</td>
<td>109</td>
<td>17</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>81 Cancer patients (16)</td>
<td>K: Normal, L: Normal</td>
<td>SR morphine</td>
<td>Oral</td>
<td>Single sample</td>
<td>29 (11–52)</td>
<td>4.6</td>
<td>6.7 (2–11) (4.6–8.7)</td>
<td></td>
</tr>
<tr>
<td>101 Cancer patients (11)</td>
<td>K: Mixed (mild), L: Normal</td>
<td>MS</td>
<td>Oral</td>
<td>Several</td>
<td>28.5</td>
<td>4.9</td>
<td>6.4</td>
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</tr>
<tr>
<td>42 Cancer patients (151)</td>
<td>K: Mixed, L: Not stated</td>
<td>Not stated</td>
<td>Oral</td>
<td>Single sample</td>
<td>32</td>
<td>6.7</td>
<td>Not calculated</td>
<td></td>
</tr>
<tr>
<td>61 Cancer patients (2)</td>
<td>K: Not stated, L: Not stated</td>
<td>MS</td>
<td>Oral</td>
<td>Multiple samples (25–46.9)</td>
<td>34.0</td>
<td>3.9</td>
<td>9.0 (2.7–5.6) (6.7–14.3)</td>
<td></td>
</tr>
<tr>
<td>80 Cancer patients (11)</td>
<td>K: Mixed (mild), L: Not stated</td>
<td>SR morphine</td>
<td>Oral (9)</td>
<td>Single sample</td>
<td>221 (8.93–94.6)</td>
<td>3.79</td>
<td>5.84 (1.61–15.0) (4.81–6.57)</td>
<td></td>
</tr>
<tr>
<td>83 Cancer patients (21)</td>
<td>K: Mixed (mild), L: Not stated</td>
<td>SC infusion</td>
<td>Single sample</td>
<td>26.9</td>
<td>3.7</td>
<td>8.7 (0.05–8) (0.18–940)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All metabolite ratios are mean molar ratios unless indicated otherwise. MS = morphine solution; Mixed = patients with normal as well as (in some studies mild) abnormal function of the organ in the group; Single sample = only one sample in each patient; Multiple samples = more than one sample in each patient during a period of increasing morphine doses; Several samples = several samples during one dosage interval in each patient. Metabolite concentrations a result of calculation of UAC or average steady-state concentration.36

31. Within 3 hr of the last oral morphine dose.
32. Blood samples at no fixed time after oral dosing.
33. Minimum 3 hours after oral dosing.
34. 4 hours after last dose of oral or SC morphine injection.
35. Median values.
to differ when comparing patients with normal renal function and patients with renal insufficiency.\textsuperscript{36,37} But in a recent study, including patients with residual renal function and requiring peritoneal dialysis, the renal excretion of morphine was found to be very low.\textsuperscript{38} The clearance of M3G and M6G have been shown to be significantly correlated with the creatinine clearance.\textsuperscript{36,38–41} This has been demonstrated in patients receiving oral or subcutaneous (SC) single dose morphine and those receiving long-term administration. Several surveys in large groups of patients have confirmed the relationship between raised creatinine and increased dose-corrected plasma concentrations of metabolites\textsuperscript{42} and metabolite:morphine ratios.\textsuperscript{43} Also, when administering IV M6G to patients with renal dysfunction, the clearance was lower and the elimination half-life longer than in a control group.\textsuperscript{44} As a consequence of the accumulation of M3G and M6G in patients with renal impairment, increased susceptibility of the toxic effects of these morphine metabolites may be seen, exemplified by respiratory depression,\textsuperscript{45–47} excessive sedation\textsuperscript{47} and myoclonic spasms.\textsuperscript{48} The clearance of M3G and M6G, and probably also morphine, is thus dependent on the renal function, and in case of impairment accumulation will arise with clinical symptoms as a consequence in severe cases.

**Other Factors Affecting Morphine Metabolism.** Factors other than hepatic and renal function may contribute to the variability in morphine metabolism. Ethnic background has been shown to have an impact on plasma concentrations of morphine. Chinese subjects, for example, have an increased clearance of morphine, which is attributable to increased glucuronidation to M3G and M6G compared to Caucasians.\textsuperscript{49} Some drugs influence UDPGT activity. An in vitro study on human liver microsomes indicated that oxazepam inhibits morphine conjugation,\textsuperscript{23} and in humans, ranitidine has been demonstrated to decrease the plasma M3G:M6G ratio.\textsuperscript{50} Also in human liver microsomal preparations, tricyclic antidepressants have been demonstrated to inhibit the morphine UDPGT.\textsuperscript{51} A clinical report emphasizes this result, having shown that tricyclic antidepressants may increase the bioavailability of morphine in cancer patients.\textsuperscript{52}

Preterm infants, even of 24–25 weeks gestation, have been shown capable of metabolizing morphine by glucuronidation, but the mean plasma clearance of morphine was 5-fold lower in neonates when compared with children aged 1–16 years.\textsuperscript{53} Plasma morphine clearance values reach adult values between one month\textsuperscript{54} and 6 months of age.\textsuperscript{55} As glucuronidation predominates in the biotransformation of morphine, the maturation of morphine clearance appears to be related to developmental differences in the UGT activity.\textsuperscript{55}

It also has been reported that elderly patients achieve more effective pain relief than young adults when given equal doses of morphine.\textsuperscript{56,57} Some studies in elderly patients have shown a reduction in the clearance of morphine in the presence of unaltered AUC for M3G and M6G.\textsuperscript{58,59} Another study demonstrated unchanged plasma morphine concentrations and increased plasma concentrations of M3G and M6G.\textsuperscript{42} Age-related reduction in hepatic and/or extrahepatic metabolism, together with a reduction in renal glomerular filtration, rate might account for these observations.

The effect of long-term treatment on morphine pharmacokinetics has received limited study. In patients receiving treatment with morphine solution, the AUC, a measure of morphine bioavailability for the individual patient, was relatively constant at three assessments during one year.\textsuperscript{60} In two studies, cancer patients receiving chronic oral\textsuperscript{61} or SC\textsuperscript{62} morphine were studied for a period of up to 8 months. Both studies concluded that the conjugation of morphine with glucuronic acid did not increase with dose or time, indicating that the metabolic pathway is not subject to autoinduction or to saturation.

**M3G and M6G**

**Pharmacokinetics of M3G and M6G**

The molecular weights of M3G and M6G are 461 and 497 gram/mol, respectively. Both compounds are polar, with $pK_a$ for the carboxylic groups of 2.83 for M3G and 3.23 for M6G.\textsuperscript{63} Glucuronides are recognized to have low protein binding and a small volume of distribution, which agrees with the pharmacokinetic properties of M3G and M6G when compared to morphine. In healthy volunteers, the plasma protein binding of M3G and M6G has
been found low, 15% and 11%, respectively,\textsuperscript{39} and the volume of distribution of M6G is lower than morphine, \textless 0.5 l/kg.\textsuperscript{64,65} Formulation of metabolites takes time, and consequently, the Tmax after morphine administration for M6G and M3G occurs later than for morphine. After administration of morphine solution, the Tmax for morphine, M3G, and M6G have been reported to be 0.5–0.75 hr,\textsuperscript{66–68} 1.5–1.6 hr,\textsuperscript{68,69} and 1.5–1.9 hr,\textsuperscript{68,69} respectively. The Tmax for morphine, M3G, and M6G after administration of extended-release morphine tablets have been reported to be 2.3–3.3 hr,\textsuperscript{66–68} 3.0–3.8 hr,\textsuperscript{68,69} and 3.2–3.7 hr,\textsuperscript{68,69} respectively.

The renal clearance of morphine has been found to be greater than the renal clearance of M3G and M6G. There is no difference in the renal clearance between the glucuronides.\textsuperscript{39}

**Blood-Brain Barrier Transport**

Clinical effects of M6G and M3G are dependent on the ability of the metabolites to reach their sites of action in the central nervous system (CNS) by passing the blood–brain barrier (BBB). Due to their highly polar, hydrophilic nature, glucuronides are generally not considered capable of crossing the BBB because of its lipophilic composition. However, it has been indicated that both the M6G molecule and the M3G molecule can exist in equilibrium between an extended and a folded form.\textsuperscript{63} The extended form predominates in polar media such as water, where it exposes the polar groups and is thus hydrophilic. In media of low polarity, such as biological membranes, the folded form prevails, hiding part of the polar groups and thus making it more lipophilic.\textsuperscript{63} Results from microdialysis studies in rats have demonstrated that after SC administration of M6G, the glucuronide was found in the brain extracellular fluid.\textsuperscript{71,72} Furthermore, after SC administration of morphine, M3G and M6G, the penetration and elimination rates in the extracellular space of the rat brain cortex have been found to be similar for all three compounds.\textsuperscript{73} After SC injection of M6G in the neonatal guinea pig, the concentration of M6G in the brain has been found to be a linear function of plasma M6G levels, suggesting that the glucuronide crosses the BBB by diffusion.\textsuperscript{74} In contrast to this, other studies in rats have demonstrated poor permeability of M6G and M3G across the BBB.\textsuperscript{75,76}

P-glycoprotein is a transmembrane protein expressed in various normal tissues, including the endothelial cells comprising the BBB. It is responsible for the efflux transport of several xenobiotics, thereby limiting their access to the organ.\textsuperscript{77} In vitro studies have demonstrated that M6G\textsuperscript{78} and morphine\textsuperscript{79} serve as substrates for this active transport system. A recent in vivo study could not demonstrate differences in analgesia in M6G-treated mice that either express or are deficient in P-glycoprotein, indicating that M6G may be such a weak substrate for P-glycoprotein that differences in analgesia are not easily detected.\textsuperscript{77} In contrast, morphine- treated mice demonstrated marked differences in analgesia depending on the presence of P-glycoprotein or not.\textsuperscript{77} The clinical implications of these findings have not yet been determined.

In humans, M3G and M6G are present in the CSF of patients receiving single as well as repeated doses of morphine. After long-term administration of morphine in cancer patients, CSF:plasma ratios for M3G and M6G are between 0.08–0.18 (M3G) and 0.07–0.15 (M6G), respectively (Table 2).\textsuperscript{27,29,80–83} In CSF, the concentrations of the metabolites may exceed those of CSF morphine (Table 2). There is thus a substantial passage of the metabolites across the BBB in humans. However, in one clinical study, it was not possible to detect measurable CSF concentrations of M6G despite its presence in plasma in several patients with unsatisfactory analgesia who were receiving oral or subcutaneous morphine, thus indicating that its passage across the blood-brain barrier may be inhibited in some patients.\textsuperscript{27} Accumulation of M6G and M3G in plasma, as seen in patients with renal failure, is associated with a progressive accumulation of these metabolites in the CSF as well.\textsuperscript{40}

**Affinity to Opioid Receptors**

M3G displays very low affinity to opioid receptors of any subtype and is thus devoid of analgesic activity.\textsuperscript{84,85} In contrast, M6G has been demonstrated to bind to opioid receptors and to be capable of eliciting profound analgesic activity.\textsuperscript{84} M6G has the same affinity for mu-1 receptors as morphine, whereas the affinity for the mu-2 receptor is 4- to 5-fold lower compared to morphine.\textsuperscript{86} M6G also labels delta and kappa receptors, but to the same low degree as morphine.\textsuperscript{84}
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<tr>
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<th>Subjects (n)</th>
<th>Kidney (K) and Liver (L) Function</th>
<th>Oral Morphine Formulation</th>
<th>Route of Administration</th>
<th>Sampling (Site) (time of sampling)</th>
<th>CSF M3G/M (range)</th>
<th>CSF M6G/M (range)</th>
<th>CSF M3G/M6G (range)</th>
<th>CSF/Plasma Morphine (range)</th>
<th>CSF/Plasma M3G (range)</th>
<th>CSF/Plasma M6G (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>59</td>
<td>Cancer patients (34)</td>
<td>K: Mixed L: Not stated</td>
<td>SR morphine</td>
<td>Oral</td>
<td>Single sample (Lu) (through)</td>
<td>34</td>
<td>4</td>
<td>7.7</td>
<td>0.79</td>
<td>(0.94–2.75)</td>
<td>0.15</td>
</tr>
<tr>
<td>81</td>
<td>Cancer patients (16)</td>
<td>K: normal L: normal</td>
<td>SR morphine</td>
<td>Oral</td>
<td>Single sample (Lu)</td>
<td>73</td>
<td>1–23</td>
<td>0.8</td>
<td>9.2</td>
<td>0.9</td>
<td>(0.5–1.7)</td>
</tr>
<tr>
<td>80</td>
<td>Cancer patients (11)</td>
<td>K: mixed (mild) L: not stated</td>
<td>SR morphine</td>
<td>Oral (9) SC (2)</td>
<td>Single sample (Lu)</td>
<td>2.39</td>
<td>0.15–1.42</td>
<td>0.42</td>
<td>6.61</td>
<td>0.14</td>
<td>(0.03–0.20)</td>
</tr>
<tr>
<td>82</td>
<td>Cancer patients (3 ventr. CSF, 8 lumbar CSF)</td>
<td>K: normal L: not stated</td>
<td>SR morphine</td>
<td>Oral (10) SC infusion (1)</td>
<td>Single sample</td>
<td>2.07</td>
<td>(0.077–0.330)</td>
<td>0.31</td>
<td>(0.126–0.481)</td>
<td>0.71</td>
<td>(0.41–1.0)</td>
</tr>
<tr>
<td>27</td>
<td>Cancer patients (16)</td>
<td>K: not stated L: not stated</td>
<td>Not stated</td>
<td>Oral or SC (number not stated)</td>
<td>Single sample (i.c.v) (not stated)</td>
<td>1.85</td>
<td>(0.05–15.23)</td>
<td>0.13</td>
<td>(0.01–0.36)</td>
<td>0.18</td>
<td>(0–1.44)</td>
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<tr>
<td>83</td>
<td>Cancer patients (21)</td>
<td>K: mixed (mild) L: not stated</td>
<td>SC infusion</td>
<td>Single sample (Lu)</td>
<td>15.0</td>
<td>0.25–99</td>
<td>0.5</td>
<td>0.015–1.7</td>
<td>0.56</td>
<td>(0.001–1.3)</td>
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</tr>
</tbody>
</table>

All metabolite ratios are mean molar ratios unless indicated otherwise.

MS = Morphine solution; Mixed = patients with normal as well as (in some studies mild) abnormal function of the organ in the group; Lu = lumbar sampling cite of CSF.

Ratios on weight basis.

Within 3 hr of the last oral morphine dose.

4 hours after last dose of oral or SC morphine.

Median values.

Blood samples at no fixed time after oral dosing.

Ventricular CSF.

Lumbar CSF.
M6G and Analgesia

The Analgesic Effect of M6G

Although substantial experimental data from animal studies have documented the analgesic effect of M6G, its potency compared to morphine has not yet been established. After SC administration of M6G to mice, M6G was only equipotent or twice as potent as morphine, but a marked increase in M6G potency was observed when administration shifted from systemic to intrathecal (IT) or ICV sites. Depending on which test was applied for assessing the analgesic response in the rat or mouse, M6G was 47 to 650 times more potent than morphine. The large difference in potency between systemically and centrally administered M6G should probably be attributed to the marked hydrophilic characteristics of this compound, which reduces its rate of penetration of the BBB. Morphine had to occupy 9.5 and 47 times more opioid binding sites than M6G after chemical visceral and thermal stimuli, respectively, to produce the same effect, suggesting that M6G has a higher intrinsic activity than morphine. Analgesia elicited by systemically administered M6G was of longer duration than after systemic morphine, which probably is the result of a 3-fold slower rate of elimination of M6G than morphine from the mouse brain. A study in rats indicated that one of the reasons for the greater ability of M6G to induce more potent central analgesia than morphine could be that M6G was predominantly trapped in the extracellular fluid, whereas morphine entered the brain cells. M6G was thus continuously available to bind quickly at opioid receptors.

Despite substantial evidence from animal studies proving the analgesic action of M6G, results from human studies are not uniform (Table 3). When applying a study design with both placebo and positive control, neither IV single administration nor short-term infusion of M6G was as potent as morphine used as a control. IV requirements for M6G used as an analgesic for postoperative pain have been assessed in post-hysterectomy patients. The group of patients exhibiting the most effective reduction in pain intensity score used a mean of 112 mg of M6G during the first 6 hours postoperatively.

The discrepancy of the findings concerning the analgesic action of M6G obtained after its administration to humans may be due to several factors. Due to the low blood–brain permeability of M6G, the compound may not reach sufficiently high CSF concentrations in order to achieve analgesia during short-term infusion. The lack of placebo or morphine controls in some studies also confound the impression of M6G as an analgesic and its potency.

The very large differences in potency between administration of IT morphine and IT M6G observed in animal studies have not been observed in human studies, although experience based on two clinical studies is too small to determine the potency ratio. Also the potency ratio between IV-administered M6G and morphine is unsolved. There was no difference in analgesia after IV administration of 5 mg/70 kg of M6G compared with 10 mg/70 kg of morphine, and doses of up to 153 mg of IV M6G during a period of 6 hours was necessary to improve postoperative pain control. As experience with administration of still larger doses of M6G is growing, a more precise concept of the dimensions of the parenteral potency factor will emerge.

The Contribution of M6G to Morphine Analgesia

What remains unsolved and still intrigues many investigators is the exact role and contri-
bution of M6G to the analgesic action seen after morphine administration. Assuming that the analgesic potency of M6G is higher than that of morphine, it would seem logical that patients with high M6G:morphine ratios (or M6G:dose ratios) would have lower pain scores than patients with low M6G:morphine ratios. Hitherto, only a few clinical studies have found evidence for M6G being a contributor to the analgesic action observed after morphine administration.97–100 Other clinical studies involving oral, SC, and epidural morphine administration have not been able to demonstrate this.29,81,83,101–103

Due to the relatively small proportion of M6G that distributes into CSF following systemic administration of morphine, the potency of the metabolite in humans or its amount in the CSF will probably have to be very high if it is to contribute substantially to morphine pharmacodynamics in patients. Furthermore, a multitude of other factors affect patients' perception of pain, including psychological factors and varying response to morphine administration due to different pain types. Lack of optimal pain control after morphine administration at the time of pain assessment and plasma sampling for determining M6G:morphine are other misleading factors.

A principal argument against clinical studies in this area is the fact that, in morphine-treated cancer patients, the main principle for regulating morphine dosage is to adjust drug dose against analgesia and side effects. A high pain score in a patient may thus reflect insufficient morphine dosage as much as a possibly low M6G:morphine ratio. This problem may be circumvented by studying morphine-naive patients. Two studies advocating for a contributory effect of M6G to total analgesia have used this. In a study on morphine-naive cancer patients, immediate-release morphine tablets were administered until sufficient analgesia was obtained on a stable dose. Results showed that an increased M6G:morphine ratio predicted lower effective serum morphine concentrations at the time of satisfactory pain relief.99

In another study,98 cancer patients receiving long-term treatment with opioids were treated with opioids other than morphine for 48 hours before the study. The patients then received an IV infusion of morphine during a mean period of 168 minutes. During and after the infusion, blood samples and pain assessments were obtained. On the basis of the average molar M6G:morphine ratios obtained during the period of morphine infusion, patients were divided into three groups. The results showed that pain relief was most pronounced in the group with the highest M6G:morphine ratio, >0.7:1.98 It should be added that one of the studies demonstrating no relationship between analgesic endpoints and M3G and M6G ratios/concentrations also used morphine-naive patients.103

A recent study in cancer patients receiving continuous infusion of IT morphine found that in CSF samples collected at fixed points during a many month long treatment course, concentrations of M6G in patients reporting effective analgesia were significantly higher than in patients with ineffective analgesia.106 Intergroup differences in M3G concentrations or M3G:M6G ratios were not significant.100

**Side Effects of M6G**

Several clinical studies have shown that administration of M6G is accompanied by fewer side effects than observed after morphine administration (Table 3). Short-term infusion of morphine or M6G in healthy volunteers in doses aiming at producing equal plasma concentrations showed significantly fewer side effects when M6G was infused compared to morphine.64 However, in other studies comparing the side effects of M6G with those of morphine, the former is seldom administered in the same doses as the latter.

**M6G and Respiration**

M6G has been demonstrated capable of inducing naloxone-reversible respiratory depression in animals.104 In rats receiving M6G, M3G, and morphine by the ICV route, M6G was approximately 10 times more potent than morphine in depressing minute ventilation.104 In awake dogs, ICV administration of M6G also caused profound dose-dependent ventilatory depression.105 In contrast, a study in humans demonstrated that single IV administration of M6G in doses up to 0.07 mg/kg did not result in respiratory depression.94,95,104 Also, IV infusion of M6G in doses up to a mean of 112 mg during 6 hours did not reduce ventilation.91,96 This may, however, be a consequence of the M6G concentrations being too low at the mu receptors in the CNS to cause respiratory de-
Table 3
Analgesic Action and Side Effects after M6G Administration

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>91</td>
<td>20 volunteers crossover, double blind</td>
<td>IV bolus + IV infusion, total amount during 4 hours: Dose A 0.04 mg/kg Dose B 0.085 mg/kg Dose C 0.13 mg/kg Dose D 0.04 mg/kg M6G + 0.34 mg/kg M</td>
<td>CO2 stimuli to nasal mucosa</td>
<td>No</td>
<td>Dose A, B, C: No resp. dep., no vom., sed. (1 pat) Dose D: No resp. dep., vom. (8 pats.), sed. (15 pats.) Dose E: Resp. dep. (2 pats.), vom. 4 pats., sed. (9 pats.)</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>37 post surgical patients, 3 groups</td>
<td>(\text{M}^{1,2}) 0.1 mg/kg IV (13 pats.)</td>
<td>Postoperative pain (knee surgery)</td>
<td>No</td>
<td>No significant difference between the 3 groups regarding nausea/vom. and resp. dep.</td>
<td></td>
</tr>
<tr>
<td>94</td>
<td>10 healthy volunteers double blind</td>
<td>(\text{M}^{1,2}) 0.014 mg/kg and 0.047 mg/kg IV (crossover) (5 volunteers) (\text{M}^{1,2}) 0.07 mg/kg IV (5 volunteers)</td>
<td>Ischemic pain test</td>
<td>Yes</td>
<td>M: nausea/vomiting (6 pats.) Sed. (10 pats.) Resp. dep. (10 pats.). M6G: No nausea/vomiting No, sed., no resp. dep.</td>
<td></td>
</tr>
<tr>
<td>92</td>
<td>3 cancer patients pretrial morphine treatment crossover, single blind</td>
<td>0.5 mg IT</td>
<td>M (0.5 mg IT)</td>
<td>Cancer pain</td>
<td>Yes</td>
<td>No cardioresp. dep. or sed. after either M6G or M</td>
</tr>
<tr>
<td>93</td>
<td>75 post-surgical patients 3 groups</td>
<td>(\text{M}^{1,2}) 0.1 mg IT (25 pats.) (\text{M}^{1,2}) 0.125 mg IT (25 pats.)</td>
<td>Postoperative pain (hip surgery)</td>
<td>Yes</td>
<td>Gr. 1 and 2: Resp. dep. (5 pats.), vom. (31 pats.) Gr. 3: No resp. dep., vom. (19 pats.)</td>
<td></td>
</tr>
<tr>
<td>95</td>
<td>20 cancer patients (opioid naive)</td>
<td>0.007 mg/kg IV (1 patient) 0.014 mg/kg IV (9 patients) 0.028 mg/kg IV (5 patients) 0.057 mg/kg IV (5 patients)</td>
<td>No</td>
<td>Cancer pain</td>
<td>Yes</td>
<td>No nausea/vom., no, sed. or euphoria, no cardiorespiratory dep.</td>
</tr>
<tr>
<td>96</td>
<td>21 post surgical patients 4 groups, single blind PCA system</td>
<td>Consumption of M6G administered by PCA (duration of assm.): (\text{M}^{1,2}) mean 13.3 mg (4 hours) (\text{M}^{1,2}) mean 31.6 mg (4 hours) (\text{M}^{1,2}) mean 47.5 mg (4 hours) (\text{M}^{1,2}) mean 112 (6 hours)</td>
<td>Postoperative pain (hysterectomy)</td>
<td>Yes</td>
<td>Nausea (2 patients) No, sed., no cardiorespiratory depression</td>
<td></td>
</tr>
</tbody>
</table>

PCA = patient controlled analgesia; Assm = assessment; M = morphine; Pat. = patient; Resp. depr. = respiratory depression; Vom. = vomiting; Sed. = sedation.
pression. Ten percent of a group of morphine-naive patients receiving IT M6G in doses of 0.1 and 0.125 mg as preoperative analgesia experienced respiratory depression, as compared to none in the IT morphine-treated group. In the absence of measurable amounts of morphine in plasma, or the presence of only very low levels, patients with renal impairment experienced respiratory depression during a period of M6G accumulation. M6G binds to the mu-1, as well as the mu-2 receptor, but has a 4- to 5-fold lower binding affinity for the latter in comparison with morphine. As the mu-2 receptor is thought to be primarily responsible for mediating respiratory depression, this could possibly explain the reduced, but not always eliminated inhibitory influence on respiration following M6G administration in humans.

**M6G and Nausea and Vomiting**

A study in ferrets has demonstrated that SC administration of M6G induced retching and vomiting at lower doses than morphine. In humans, results on the emetic potential of M6G are contradictory. Single IV administration of M6G in doses of half the size of morphine dosage resulted in absence or lower frequency of nausea and vomiting. On the other hand, when used as perioperative analgesia, IT administration of M6G in doses one-fourth to one-fifth of IT-administered morphine resulted in high and equal frequencies of nausea and vomiting. Accumulation of M6G in plasma, as seen in morphine-treated patients with renal insufficiency, has also been associated with nausea. The discrepancy between the observations may be caused by differences in concentrations of M6G present at the emetic chemoreceptor trigger zone in the medulla and/or different designs of the studies.

**M6G and Dryness of the Mouth**

Dryness of the mouth is one of the most frequent side effects observed in patients in morphine treatment, but as it seldom implies severe drawbacks for the patients, it has not received much attention. A study in healthy volunteers measured the degree of salivation after morphine administration as either IV infusion, immediate-release tablets, or controlled-release tablets and found that reduction in salivation was most pronounced at the high plasma concentrations of morphine obtained after IV administration of the drug. Also, in a clinical study of cancer patients, it was demonstrated that patients reporting dry mouth had higher morphine concentrations in plasma than patients not reporting dryness of the mouth.

**M3G and Antagonism of Antinociception**

M3G is considered to be devoid of any analgesic activity. In fact, it has been discussed if it antagonizes the analgesic effect of morphine and M6G, and plays a role in the development of tolerance. Evidence both pro and con for this hypothesis arises from studies in animals, as M3G, to our knowledge, never has been administered to humans. Results from these studies, which almost exclusively have been performed in rats, which are unable to metabolize morphine to M6G, are conflicting. In some studies, M3G has been demonstrated to antagonize morphine or M6G analgesia. SC or ICV administration of M3G prior to or after administration of morphine has been shown to reduce the antinociceptive response of the two analgesic agents. Another study in rats demonstrated a highly inverse correlation between the level of antinociception and mean plasma M3G morphine concentration after IV infusion of morphine. Administration of equipotent doses of M6G and morphine during several days in
mice induced declining antinociception. But when inhibiting the production of M3G from morphine by treatment with clofibrate, subsequent administration of M6G maintained its antinociceptive activity, implying that M3G probably antagonizes this effect of M6G.112 In contrast, other studies in rodents have not found any influence by M3G on morphine analgesia.116–118 One study has even showed that co-injection of M3G and morphine increased and prolonged analgesia beyond that seen with morphine alone (Table 4).119

In humans, there are only few studies concerned with the possible role of M3G as an antianalgesic agent, or one involved in the development of tolerance. It has been suggested that patients’ analgesic response to morphine depends on their M3G:M6G ratio,120 but clinical evidence for this hypothesis is lacking. In eleven cancer patients with very poor pain relief despite oral or SC morphine administration, the M3G:M6G ratios in plasma and CSF were found to be similar to patients with well-controlled pain, implying that M3G does not play a role in morphine-insensitive pain.80

M3G and Hyperalgesia, Alloodynia, and Myoclonus

Apart from its possible role as an antianalgesic, M3G and high-dose morphine have also been connected to symptoms such as hyperalgesia, allodynia, and myoclonus. Several studies in rodents have found that M3G and high-dose morphine administered by the ICV,114,121–123 as well as the IT,124–126 route produced symptoms of altered pain behavior, such as hyperalgesia, allodynia, and motor excitation in the shape of “wet dog shakes”, seizures, and even death.

The mechanisms behind the neurotoxic phenomena are not fully elucidated, and there is still much controversy concerning the etiology. Some animal studies have demonstrated reversibility of this opioid-induced neuroexcitation by naloxone,123,127 whereas others have found no effect of the opioid antagonist,124–126 indicating that a non-opioid receptor mechanism is involved. In support of the latter, it has been demonstrated in animal studies that the central excitatory potency of a compound is enhanced as opioid receptor binding is diminished; M3G is several hundred times more potent than morphine in evoking hyperactive motor behavior.121

In animals, it has been shown that the behavioral excitation of high-dose morphine and M3G can be mimicked by the glycine antagonist strychnine.125 Glycine receptors play a role in regulating the ongoing encoding of afferent stimuli and are thus important for maintaining normal sensory processing. It has been speculated that M3G or high doses of morphine may elicit the symptoms of hyperalgesia and myoclonus by reducing the influence of the inhibitory glycinergic mechanisms in the spinal cord. However, an in vitro study showed that M3G and morphine did not inhibit the binding of 3H-strychnine in the spinal cord, suggesting that none of them causes their excitatory effects by antagonizing glycine at strychnine-sensitive glycine receptors.85

Activation of the N-methyl-D-aspartate (NMDA) receptor has been shown to have multiple effects on opioid receptor-mediated functions, such as antinociception and tolerance. Administration of NMDA antagonists have been demonstrated to cause reduction of behavioral excitation caused

<table>
<thead>
<tr>
<th>Reference</th>
<th>M3G Administration in Relationship to Morphine or M6G Administration</th>
<th>Animal</th>
<th>Route</th>
<th>Morphine</th>
<th>M6G</th>
</tr>
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<tr>
<td>114</td>
<td>prior, after</td>
<td>rat</td>
<td>ICV</td>
<td>reduced</td>
<td>reduced</td>
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<tr>
<td>113</td>
<td>prior</td>
<td>rat</td>
<td>ICV and IT</td>
<td>–</td>
<td>reduced</td>
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<tr>
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<td>prior</td>
<td>mice</td>
<td>SC</td>
<td>no effect</td>
<td>reduced</td>
</tr>
<tr>
<td>116</td>
<td>prior</td>
<td>mice</td>
<td>ICV intraperitoneal</td>
<td>no effect</td>
<td>no effect</td>
</tr>
<tr>
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<td>prior</td>
<td>rat</td>
<td>IT</td>
<td>no effect</td>
<td>–</td>
</tr>
<tr>
<td>118</td>
<td>prior</td>
<td>rat</td>
<td>IV</td>
<td>no effect</td>
<td>–</td>
</tr>
<tr>
<td>119</td>
<td>co-injection</td>
<td>rat</td>
<td>IV</td>
<td>increased</td>
<td>–</td>
</tr>
</tbody>
</table>
by ICV,122 or IT-administered128 high-dose morphine or M3G, and it has been suggested that activation of NMDA receptors play an important role in eliciting the excitatory symptoms.128 As in vitro binding studies have shown that M3G has very low affinity for the known binding sites on the NMDA receptor complex, the NMDA antagonists may act as functional antagonists of the excitatory effects of M3G.122

Clinically, the symptoms of hyperalgesia, allodynia, and myoclonus have mostly been observed in cancer patients treated with morphine primarily in high doses administered by several different routes.48,129–133 In several of the case reports describing these symptoms, very high plasma levels of morphine and M3G,48,130 as well as accumulation of M3G relative to morphine48 or M6G,129,130 has been demonstrated. Although the role of morphine and M3G in eliciting hyperalgesia, allodynia, and myoclonus have not been clearly established in humans, a relationship between discontinuation of morphine and disappearance of the side effects has been observed.130,134

M3G and Respiration

Studies in rats104 and dogs105 have demonstrated that ICV administration of M3G caused stimulation of ventilation. Furthermore ICV administration of M3G functionally antagonized the ventilatory depression induced by M6G in rats.113

In humans, there are no reports of M3G stimulating respiration. In several case reports of respiratory depression in morphine-treated patients, accumulation of M6G and M3G has been observed in the presence of renal impairment.45–47 The very high plasma levels of M3G were apparently not able to counteract the respiratory depressant effects of M6G. The M3G: M6G ratios in two of the studies45,47 were within the ranges observed in patients with normal renal function (Table 1), but lower, 0.5–2.0, in the third study.46

Conclusions

Factors affecting pain relief and possible side effects experienced by the individual patient treated with opioids are multitudinous. They include the pharmacokinetic variation among individuals, the possible effects of active metabolites, development of tolerance, differences in pain pathophysiology, dynamics of pain intensity, as well as psychological and social components. Physicians dealing with opioid-treated patients may be well aware of all these factors, but have no precise idea of their rank of importance within the individual.

Morphine is and will probably remain the most used analgesics worldwide for many years to come. A multitude of animal and clinical studies point out that its two most prominent metabolites, M3G and M6G, exert effects of their own, and the question arises as to the degree to which they influence pain treatment outcomes. Are these compounds important elements in the total array of effects observed after morphine administration and may their presence in varying concentrations at least partly explain the differences and difficulties in providing sufficient analgesia by morphine treatment? Or is their importance so negligible that their effects disappear among all the other factors affecting analgesia and side effects after morphine administration? Despite intensive research the precise contribution of these major metabolites of morphine to its global effects remains unknown at present. Thus, further research within this area should be directed towards 1) establishing the potency factor of M6G compared to morphine—this will enable a more exact determination of the contribution of M6G to the analgesic effect observed after morphine administration; and 2) obtaining a greater knowledge of the kind and degree of side effects directly attributable to M6G and M3G, with special reference to the neurotoxic side effects, hyperalgesia, allodynia, and myoclonus.

References


5. Vater M, Smith G, Aherne GW, Aitkenhead


110. Westerling D, Persson C, Höglund P. Plasma concentrations of morphine, morphine-3-glucuronide and morphine-6-glucuronide after intravenous and oral administration to healthy volunteers; relationship to nonanalgesic actions. Ther Drug Monit 1995;17:287–301.


122. Barlett SE, Cramond T, Smith MT. The excitatory effects of morphine-3-glucuronide are attenuated by LY274614, a competitive NMDA receptor antagonist, and by midazolam, an agonist at the benzodiazepine site on the GABA<sub>δ</sub> receptor complex. Life Sci 1994;54(10):687–694.


