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Morphine-6-glucuronide is responsible for the analgesic effect after morphine administration: a quantitative review of morphine, morphine-6-glucuronide, and morphine-3-glucuronide

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Editor's key points

- Morphine has a number of active metabolites, with variable analgesic effects.
- By analysing published pharmacological data, the effects of morphine and morphine-6-glucuronide (M6G) were compared.
- Assessing all routes of administration, M6G was found to contribute significantly to analgesia.
- When renal function is impaired, M6G may accumulate, with an increase in its effects.
- Further prospective work is needed to explore the effects of morphine metabolites.

Background. Morphine-6-glucuronide (M6G) is a strong μ-receptor agonist with higher affinity than morphine itself. It has been suggested that M6G contributes to the analgesic effect after administration of morphine, but the extent of its contribution remains unclear.

Methods. In order to elucidate the relative contribution of both drugs to the overall analgesic effect mediated by the μ-receptor, published data on μ-receptor binding, plasma protein binding, concentrations [preferably area under the concentration–time curve (AUC)] of morphine and M6G in blood or cerebrospinal fluid (CSF), or concentration ratios were used to calculate free CSF concentration corrected for receptor binding for each compound. To compare different routes of administration, free CSF concentrations of M and M6G corrected for potency were added and compared with oral administration.

Results. Based on AUC data, there is a major contribution of M6G to the overall analgesic effect; the mean contributions being estimated as 96.6%, 85.6%, 85.4%, and 91.3% after oral, s.c., i.v., and rectal administration of morphine, respectively. In patients with renal insufficiency, 97.6% of the analgesic effect is caused by M6G when morphine is given orally. Owing to accumulation of M6G over time in these patients, morphine may be regarded as a prodrug.

Conclusions. When administering morphine to patients, the analgesic effect is mainly caused by M6G instead of morphine itself, irrespective of the route of administration. Therefore, the patient's kidney function plays a key role in determining the optimal daily dose of morphine.

Keywords: analgesia; morphine; morphine metabolism; morphine pharmacokinetics

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Morphine is a μ-opioid analgesic used in the management of moderate-to-severe cancer and postoperative pain. The μ-receptors located in the central nervous system (CNS) are responsible for supraspinal analgesia, respiratory depression, and sedation.[1] Morphine undergoes metabolism (Supplementary Appendix S1) to morphine-3-glucuronide (M3G) (57.3%) and morphine-6-glucuronide (M6G) (10.4%)[2 3] by UGT2B7[4] in the liver. Both metabolites are cleared by the kidneys and accumulate in renal failure.[5–8] While morphine has a low plasma protein binding of 35%, the binding for M3G and M6G is reported to be even lower with 10% and 15%, respectively.[9]

Numerous studies can be found reporting concentrations of morphine and its metabolites M3G and M6G in plasma, CSF, or both.[10–15] Both morphine glucuronides cross the blood–brain barrier, but the penetration rate is lower for M3G and M6G than for morphine itself.[16] Pharmacokinetic studies indicate substantially higher plasma concentrations of the two metabolites than those of morphine (M3G/morphine: 34; M6G/morphine: 3.9).[17]

The role of M6G as a strong agonist at the μ-receptor is widely accepted.[18–21] It has been claimed that about 85% of the analgesic effect of morphine is derived from M6G.[11] In contrast, M3G has an up to 200 times lower μ-receptor binding compared with morphine[22] and is devoid of analgesic activity, although some studies have reported an antagonistic activity[20 23 24] or a weak agonist activity.[25]

With this investigation, we aimed to elucidate the relative contributions of morphine and its active glucuronide metabolite

M6G to the overall analgesia obtained after administration of morphine. This might help to explain the large dose range of morphine in pain patients.

Methods

The rationale was to assemble, classify, and analyse existing studies which reported on morphine, M3G, and M6G. Therefore, a database research [PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez), pubChem (http://www.ncbi.nlm.nih.gov/pccompound), drugbank (http://www.drugbank.ca/)] was performed to identify *in vivo* and *in vitro* studies which dealt with morphine, M3G, M6G, and their concentrations in blood and cerebrospinal fluid (CSF) (Supplementary Appendix S2). Also μ-receptor binding studies were included. In Tables 1 and 2, all included studies and the data extracted are listed. All data extracted from the studies were first arranged for the different routes of administration of morphine. The concentration data were converted into molar units (nmol litre^{-1}) using the molar masses of the compounds (M: 285.34 g mol^{-1}; M3G: 461.46 g mol^{-1}; M6G: 461.46 g mol^{-1}).

Where available, plasma AUC (area under the concentration–time curve) data of the compounds were used as a measure of exposure. Additionally, the ratios M3G/M, M6G/M, and M3G/M6G in plasma, in CSF, or both were given. However, in some studies, only the ratios and no concentrations were reported. Other studies published only maximum concentrations (C_{max}). Finally, occasionally, only mean concentration data were reported with no closer characterization. Only seven studies provided brain/plasma ratios for morphine and M6G; therefore, these data were averaged for further calculations.

Based on plasma exposure data (AUC; C_{max}; mean concentration), plasma concentration ratios (M6G/M), plasma protein binding, brain/plasma ratio, concentrations in CSF, and the potencies of the compounds, the relative contributions of morphine and M6G to the overall effect have been calculated (Fig. 1) using the following equations:

$$\text{Brain concentration (nmol litre}^{-1}) = \text{blood concentration (nmol litre}^{-1}) \times \text{brain/plasma ratio}$$

$$\text{Free brain concentration (nmol litre}^{-1}) = \text{brain concentration (nmol litre}^{-1}) \times \text{free fraction brain}$$

$$\text{Free brain concentration corrected for potency} = \text{free brain concentration} \times \text{relative potency of morphine or M6G (morphine = 1)}.$$

In some studies, only plasma or CSF concentration ratios (M6G/M) were given. These data were also used to calculate the M6G concentration relative to morphine. Furthermore, a comparison between the different routes of administration was carried out. Only those studies where the dose was specified could be used. After dose normalization, free brain concentrations of M and M6G corrected for potency were added and compared with oral administration.

We decided to use a rather simplistic approach rather than performing a meta-analysis as the studies and their data are extremely heterogeneous and the studies analysed were carried out over a long period of time with different analytical methods used.

Results

The basic data used for the calculations like μ-receptor affinity and protein binding for morphine and M6G are shown in Table 1. Concentration data and/or ratios of 23 studies with morphine and its glucuronides were analysed (Fig. 2).

Reported data on C_{max}, AUC, and mean concentrations showed large variations because of different routes of administration, variable doses, and heterogeneous study participants (Table 2). However, when calculating the relative contributions of morphine and M6G to the overall effect, data are very consistent regardless of the morphine doses used or the pharmacokinetic parameter reported (Table 3).

M6G contributes largely to the analgesic effect obtained after morphine administration with a minor role of morphine itself. However, based on AUC data (Table 3), the relative contribution of M6G to the overall effect is, to a certain degree, dependent on the route of morphine administration with 96.6%, 85.6%, 85.4%, and 91.3% after oral, s.c., i.v., and rectal administration. A lower contribution of M6G was noted after i.m. (68.3%) administration of morphine. No large differences were observed when the calculation was based on the mean concentration data or M/M6G ratio in plasma. However, C_{max} values showed differences after i.v. and s.c. administration.

About 80% of the total analgesic effect results from M6G when morphine is given i.v. as a single dose (Table 4). In

Table 1 Data of morphine and M6G used for the calculations performed. SD, standard deviation; NA, not available

	μ-Affinity (nM)[26]	Rel. potency	Protein binding (%)[9]	Free fraction	Free fraction brain[27]	Mean (SD) brain/plasma ratio (7 studies)[9 11 13 14 15 28 29]
Morphine	1.2	1	35	0.65	0.405	0.41 (0.32)
Morphine-6-glucuronide	0.6	2	15	0.85	NA	0.56 (0.88)
Morphine-3-glucuronide	37.1	0.032	10	0.90	NA	0.16 (0.18)