

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 UGT2B7⁴ 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 morphine²² 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: $285.34 \text{ g mol}^{-1}$; M3G: $461.46 \text{ g mol}^{-1}$; M6G: $461.46 \text{ g mol}^{-1}$).

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:

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

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

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

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)

Table 2 Pharmacokinetic data and doses (morphine base) reported in the studies used for the analysis. CR, controlled release; IR, immediate release; CRM, morphine sulphate controlled-release; MSER, morphine sulphate extended release; s.c.b., subcutaneous bolus injection; s.c.i., subcutaneous infusion

Study	Information	Route, dose (mg)	AUC blood (h nmol litre ⁻¹)	C _{max} blood (nmol litre ⁻¹)	Mean blood (nmol litre ⁻¹)	CSF conc. (nmol litre ⁻¹)	Brain/plasma ratio	M6G/M blood	M6G/M brain
Christrup and colleagues ³⁰	18 patients chronic and cancer pain. Data for different tablets (CR, IR)	p.o. CR, 114	M: 99; M6G: 548	M: 32.8; M6G: 152.1				5.9	
		p.o. IR	M: 98; M6G: 538	M: 38.9; M6G: 135.7				6	
Dale and colleagues ²⁸	38 patients for hip replacement	i.v., 8.88	M: 655.5			M: 1.663 min nmol litre ⁻¹	M: 0.18		
		i.m., 8.88	M: 780			M: 1.109 min nmol litre ⁻¹	M: 0.09		
Du and colleagues ³¹	6 cancer patients	p.o., 22.6	M: 434.3; M6G: 1205.6	M: 156.2; M6G: 270.2				3.28	
		Rectal, 11.25	M: 574.8; M6G: 1020	M: 112.8; M6G: 181				2.15	
Goucke and colleagues ¹⁰	11 cancer patients	p.o./s.c., 205			M: 193; M6G: 847	M: 200; M6G: 115	M: 1.04; M6G: 0.14	3.79	0.42
Hand and colleagues ¹¹	15 patients undergoing transurethral prostatectomy	p.o., 22.6		M: 106; M6G: 102		M: 42; M6G: 77	M: 0.4; M6G: 0.75		
		i.m., 7.44		M: 99; M6G: 37		M: 74; M6G: 84	M: 0.75; M6G: 2.27		
Hoffman and colleagues ³²	11 cancer patients	p.o., 30			M: 53.1; M6G: 143.4			0.78	
		i.v., 10			M: 92.3; M6G: 119			1.36	
Holthe and colleagues ³³	70 cancer patients	p.o., 170			M: 126; M6G: 731			7.2	
Klepstad and colleagues ²⁹	40 cancer patients. Data for different tablets (CR, IR)	p.o. CR, 97		M: 99; M6G: 287	M: 64; M6G: 219			5.2	
		p.o. IR, 97		M: 76; M6G: 297	M: 66; M6G: 257			5.4	
Meineke and colleagues ¹²	9 neurological/neurosurgical patients	i.v., 20		M: 1049.28; M6G: 557.14		M: 71.49; M6G: 9.53	M: 0.068; M6G: 0.017		
Moolenaar and colleagues ³⁴	25 cancer patients	p.o., 22.3	M: 455.6; M6G: 1807.3	M: 57.48; M6G: 299.71					
		Rectal, 22.3	M: 704.42; M6G: 1300.22	M: 108.64; M6G: 160.36					
Osborne and colleagues ³⁵	10 volunteers	i.v., 10	M: 228.7; M6G: 313.4	M: 273.2; M6G: 79.5				1.4	
		p.o., 10	M: 42.9; M6G: 371	M: 20.9; M6G: 83.9				9.7	
Osborne and colleagues ⁵	4 groups: healthy (10 patients), 3 different groups of renal failure (8, 9, 9 patients)	i.v. healthy, 5.37	M: 228.7; M6G: 313.4	M6G: 79.5					
		i.v. no dialysis, 5.2	M: 398; M6G: 2885.8	M6G: 160.2					
		i.v. dialysis, 5.14	M: 469.1; M6G: 2763	M6G: 140.7					
		i.v. transplantat, 4.7	M: 302.1; M6G: 876.1	M6G: 114.5					
Pauli-Magnus and colleagues ⁷	10 CAPD patients (renal failure)	i.v., 7.59	M: 369.3; M6G: 4302					12.2	

Continued

Table 2 Continued

Study	Information	Route, dose (mg)	AUC blood (h nmol litre ⁻¹)	C _{max} blood (nmol litre ⁻¹)	Mean blood (nmol litre ⁻¹)	CSF conc. (nmol litre ⁻¹)	Brain/plasma ratio	M6G/M blood	M6G/M brain
Peterson and colleagues ³⁶	21 cancer patients	p.o./ s.c., 110			M: 126.17 M6G: 308.37			7.2	
Portenoy and colleagues ³⁷	10 patients with chronic pain. Data for different tablets (CR)	p.o. CRM, 191	M: 1093.43; M6G: 5868.33	M: 91.47; M6G: 455.1					
		p.o. MSER, 218	M: 1132; M6G: 5978.85	M: 74.3; M6G: 364.1					
Poulain and colleagues ¹³	2 cancer patients	p.o., 14.88	M: 124; M6G: 1248.5	M: 53.5; M6G: 277		M: 8.5; M6G: 41	M: 0.16; M6G: 0.15		
Sakurada and colleagues ³⁸	26 cancer patients	p.o., 60			M: 158.76; M6G: 86.68			1.23	
Stuart-Harris and colleagues ³⁹	6 healthy volunteers	s.c.b., 3.7	M: 303; M6G: 252	M: 262; M6G: 62.2				1.19	
		s.c.i., 3.7	M: 198; M6G: 171	M: 46; M6G: 30.1				1.28	
		i.v., 3.7	M: 269; M6G: 259	M: 283; M6G: 66.7				1.33	
Van Dongen and colleagues ⁹	16 cancer patients	p.o., 227					M: 0.9; M6G: 0.09	4.6	0.8
Westerling and colleagues ⁴⁰	12 healthy volunteers	i.v., 7.59			M: 410; M6G: 85			1.23	
Westerling and colleagues ⁴¹	14 healthy volunteers. Data for different tablets (CR, IR)	i.v., 7.59		M: 386.5; M6G: 91.1				1.4	
		p.o. IR, 22.77		M: 23.6; M6G: 117.8				6.4	
		p.o. CR, 22.57		M: 16.7; M6G: 102				5.4	
Wolff and colleagues ¹⁴	34 cancer patients	p.o. slow release, 142			M: 78.85; M6G: 725.96	M: 44.86; M6G: 90.15	M: 0.79; M6G: 0.15	23	5.1
Wolff and colleagues ¹⁵	21 cancer patients	s.c., 48			M: 392; M6G: 935	M: 34.7; M6G: 14	M: 0.36; M6G: 0.1	3.4	0.5

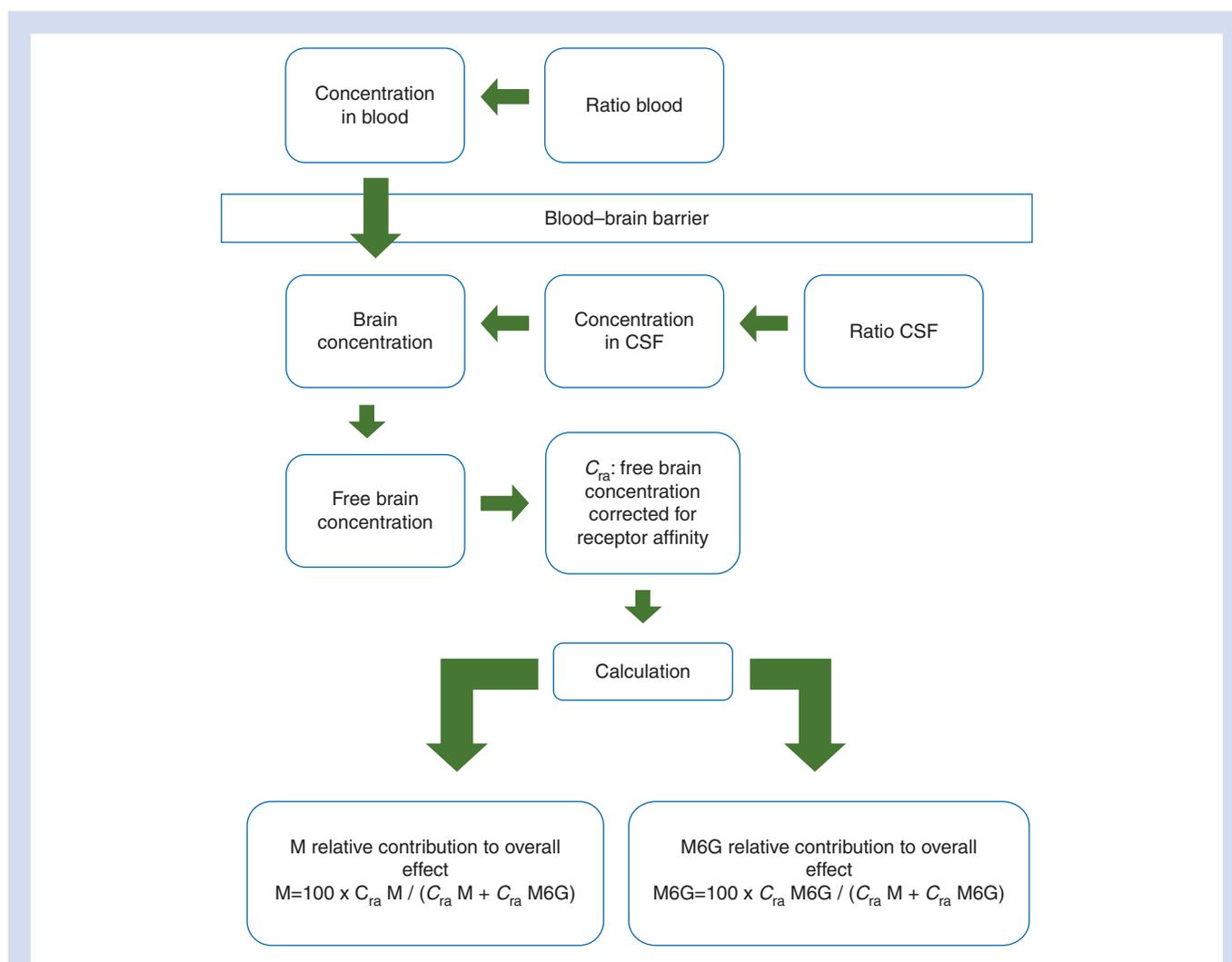


Fig 1 Flowchart to demonstrate the calculation of the relative contribution of morphine and M6G depending on the parameter available.

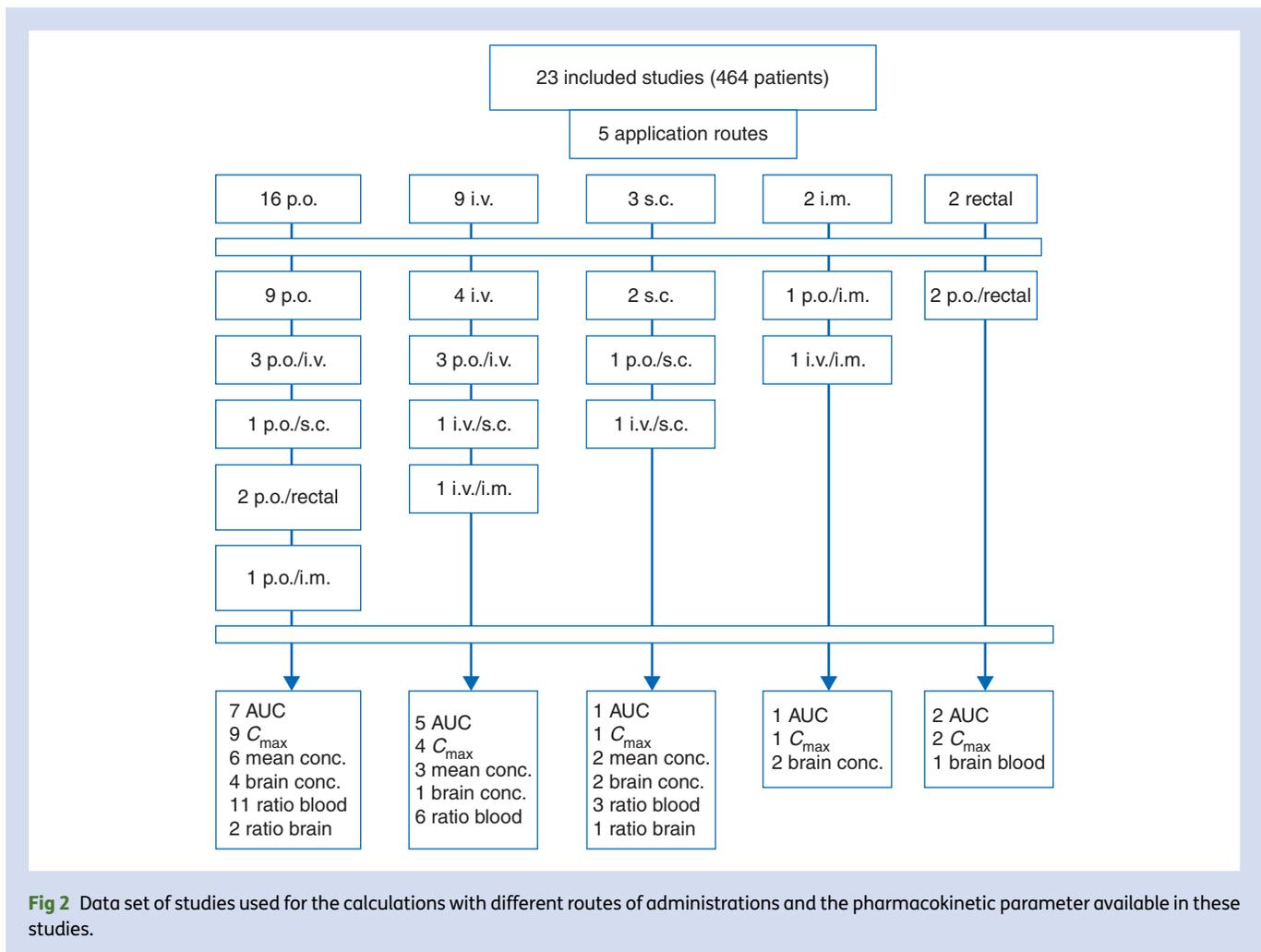
patients with renal insufficiency, 97.6% of the analgesic effect was caused by M6G when morphine is given orally (Table 4). Both M6G and M3G accumulate in patients with renal failure, because clearance of these two metabolites is related to creatinine clearance and renal function.^{7 43} Therefore, an even higher contribution of M6G to the analgesic effect will occur after multiple administration of morphine.

Based on the calculated data, the dose equivalence of morphine using different routes of administration shows that oral morphine should be used at similar doses as i.v. morphine to gain the same analgesic effect (Table 3). There was only one study where i.v. and p.o. administration were applied to the same subjects and based on AUC data, the relative doses for the same effect are calculated to be 1:1.1 (p.o.:i.v.).³⁵ When the comparison between i.v. and p.o. administration was based on reported C_{max} concentrations, on average 3.7-fold higher oral doses are needed to elicit the same μ -opioid effect. Regarding rectal and i.m. administration, almost the same doses can be used as after oral administration (Table 3).

Discussion

Based on the calculations presented, **M6G is the dominating factor** in the overall **analgesic effect** obtained after morphine administration. To some degree, this has been suggested earlier that M6G may play a large role for the effect after morphine administration,^{4 25 35} and this was based mainly on relative plasma concentration data.

Because of the fact that morphine has been used as an analgesic substance for a long time, a large number of publications were found. Close inspection revealed a large variability in given pharmacokinetic data from all publications. This may, at least in part, be due to the specificity of the analytical methods being used. Also, in many studies, only morphine concentrations were measured and these could not be used for the calculations performed in the current investigation because data on blood or brain concentrations of morphine and its metabolites are necessary. Frequently, only C_{max} or unspecified mean blood concentrations were published, especially in older publications.^{14 15 32 36 40} The included studies with all data



required for the calculations were carried out in different decades with different analytical methods. This might also contribute to the large variability and decreases the comparability of the studies. A systematic review of 57 studies shows a wide range of the ratio of M6G to morphine (0–97).⁴⁴ Another investigation with 175 patients with normal renal and hepatic function who received chronic oral morphine therapy demonstrated a broad unimodal distribution of M6G to morphine: 0.5–72.8.⁴⁵ Morphine is exclusively metabolized by UGT2B7.⁴⁶ A factor contributing to the large variability of M6G to morphine ratio might be the presence of several single-nucleotide polymorphisms in the coding and regulatory regions of human UGT2B7 gene, which give rise to four different haplotypes and seven genotypes. However, no relationship between polymorphisms and the ratio has been established, implying that other unidentified factors are responsible for the variability in M6G to morphine ratios.⁴⁵

A surprising outcome of our calculations is the similar potency obtained for the different routes of administration. It is current understanding that a three-fold higher oral morphine dose in comparison with i.v. morphine is needed for the same analgesic effect.⁴⁷ However, our calculations based on free brain exposure of morphine and M6G corrected for receptor

affinity using blood AUC data revealed that similar doses should be used for p.o. and i.v. administration. A possible explanation could be the fact that after p.o. administration of morphine, the proportion of M6G is higher than after i.v. treatment (Table 2). Certainly, a constraint is the heterogeneity of the i.v. administration with morphine in the studies mostly administered as an i.v. bolus injection^{5 28 32 35 39} or as an infusion over a period of 10–30 min.^{7 12 40 41} This does not reflect the i.v. morphine treatment in chronic pain patients. Therefore, the results obtained from the performed calculations for i.v. and p.o. administration may differ from the clinical setting, where usually three-fold higher doses of oral morphine compared with the parenteral route are administered. Interestingly, when the calculations were based on reported C_{max} concentrations for morphine and M6G after p.o. and i.v. administration, the p.o. morphine dose should be almost four-fold higher than the i.v. dose. Therefore, an important factor seems to be the input rate of the drug which is much faster after i.v. administration resulting also in different AUC to C_{max} ratios depending on the route of administration. For other routes of administration like i.m. and rectal where the input rate is similar to oral administration, the dose requirements are similar to oral morphine (about 1:1). Especially for routes

Table 3 Contribution of morphine and M6G to the overall analgesic effect. *Calculation made with only one available study

route of administration	Mean relative contribution to overall effect (%) (range)		Relative efficacy p.o. = 1 Ratio p.o.: other route
	Morphine	Morphine-6-glucuronide	
p.o.			
AUC	3.4 (1.7–5.9)	96.6 (94.1–98.3)	
C _{max}	5.1 (2.8–15.3)	94.9 (84.7–97.2)	
Mean conc.	7.9 (1.8–24.1)	92.1 (75.9–98.2)	
Ratio	3.8 (0.7–12.4)	96.2 (97.6–99.6)	
i.v.			
AUC	14.6 (11.2–21.4)	85.4 (78.6–88.8)	1:1.1
C _{max}	41.6 (24.6–62.0)	58.4 (38.0–75.4)	1:3.7
Mean conc. ³²	11.8*	88.2*	1:2.65
Ratio	11.5 (11.0–12.6)	88.5 (87.6–89.0)	
s.c.			
AUC	14.4 (12.0–16.9)	85.6 (83.1–88.0)	
C _{max}	25.9 (11.4–40.5)	74.1 (59.5–88.6)	
Mean conc. ¹⁵	6.8*	93.2*	
Ratio	8.5 (4.5–12.7)	91.5 (87.3–95.5)	
Rectal			
AUC	8.7 (8.6–8.9)	91.3 (91.1–91.4)	1:1.6
C _{max}	10.1 (9.7–10.5)	89.9 (89.5–90.3)	1:1.8
Ratio ³¹	7.5*	92.5*	
i.m.			
Mean conc. ¹¹	31.7*	68.3*	1:0.72

Table 4 Contribution of morphine and M6G in renal failure to the overall analgesic effect

Study	Way of application route	Relative contribution (%)	
		Morphine	Morphine-6-glucuronide
Osborne and colleagues (no dialysis) ⁵	i.v.	19.2	80.8
Osborne and colleagues (dialysis) ⁵	i.v.	22.7	77.3
Pauli-Magnus and colleagues ⁷	i.v.	12.9	87.1
D'Honneur and colleagues ⁴²	p.o.	2.4	97.6

of administration with fast input rates, AUC seems not to be a valid parameter for the calculation of dose equivalences.

Data about morphine therapy in patients with renal dysfunction are scarce. But the few available studies (Table 4) show that in patients with renal dysfunction, M6G is responsible for 77–87% of the analgesic effect after single-dose i.v. treatment, which is similar to patients with normal renal function. After single oral morphine administration, this increases to >90%.⁴² Therefore, in patients with renal dysfunction, the contribution of M6G for the analgesic effect will increase to 100% after multiple dose treatment, because of accumulation of the glucuronides. These findings may also be an explanation of why those patients report side-effects more often.^{5, 48}

The analgesic effects of M6G in man have been demonstrated by i.v.^{49–51} and intrathecal administration.^{52, 53} According to the available literature, some studies found no analgesic effect of M6G during short-lasting and low-dose i.v. use of

M6G,^{54, 55} while other studies identified an analgesic effect of M6G.^{50, 51, 56, 57} Higher doses of M6G (0.2 and 0.3 mg kg⁻¹ in contrast to lower doses 0.05–0.1 mg kg⁻¹) produced effective and long-lasting analgesia.^{8, 58} One study showed a similar effect of M6G and morphine for analgesia after i.v. infusion and subsequent s.c. patient-controlled analgesia with no significant differences between M6G and morphine doses.⁵⁹ The onset time of the analgesic effect of morphine and M6G was nearly equivalent (30 min) after i.v. administration.⁶⁰ Comparing the effects of M6G with morphine in different animal tests, M6G was up to 360 times more potent.^{61–63} Our calculations are based on both substances present; in this case, the measured M6G plasma concentrations formed by metabolism from morphine which exceed those of morphine itself (Table 2).⁶⁴

After M6G administration, the side-effects are similar to those observed after morphine administration,^{8, 64–66} but some found that M6G is devoid of or has less side-effects

such as nausea, vomiting, sedation, and respiratory depression.^{50–52 57 59} In a study with six healthy volunteers, no nausea, itching, or rash was observed after M6G in contrast to morphine administration.⁶⁷ In a study with patients, the frequency of nausea after M6G was only half of that after morphine administration and there was a clear difference in somnolence favouring M6G.⁵⁹

Both M6G and morphine do not easily cross the blood–brain barrier, being substrates of the efflux transporter P-glycoprotein which was recently reviewed.⁴ Because of the **hydrophilic nature of M6G in comparison with morphine, the passage across the blood–brain barrier is relatively slow compared with morphine.**^{68 69} The higher plasma concentrations of M6G achieved after morphine administration (Table 2) result in a larger concentration gradient across the blood–brain barrier and allows penetration of M6G into the brain. Hence, after binding to the μ -opioid receptors, analgesia is produced.^{8 70}

Although only limited data are available on the kinetics, blood–brain barrier penetration, analgesic, and side-effects of M6G, the evidence of its potent analgesic action and favourable side-effect profile is generally accepted. In a placebo-controlled study, **M6G showed an analgesic potency of 2:1 compared with morphine which was associated with less respiratory suppression.**⁵⁷ It can be suggested from the data presented and the current literature that **morphine is essentially a prodrug with respect to the analgesic effect, but morphine produces unwanted effects like nausea, vomiting, and respiratory depression.**

Regarding μ -receptor binding, M3G has a much lower affinity than M6G or morphine itself.²⁶ The K_i values used for our calculations are 1.2 nM (morphine), 37.1 nM (M3G), and 0.6 nM (M6G), respectively.²⁶ According to the literature, the receptor binding of M6G is at least comparable with morphine if not higher than morphine.^{71–73}

Other receptor binding studies reported even lower affinities for M3G (K_i : 360–6100 nM).^{18 22 74} It might also be possible that M3G does not bind to the receptor at all, and the explanation for still having receptor binding could be a result from contamination of the M3G used in the studies by morphine.⁷⁴ However, the plasma concentrations of M3G are the highest compared with M6G and morphine itself. Therefore, unspecific receptor binding could be possible but has not yet been proven. Although it is not clear whether it binds to the receptor, it is also unknown if M3G acts as a receptor agonist or antagonist, but it has been claimed that M3G is responsible for side-effects and pain enhancement,⁷⁵ especially after accumulation in patients with renal dysfunction. Performing a calculation of the relative contribution including M3G, the results showed that <4% of the total effect might be attributed to M3G. Hence, the role of M3G for the analgesic effect of morphine is probably insignificant. This is supported by animal studies where high doses of M3G (27.6 mg kg⁻¹) injected intracerebrally showed no analgesic effect.⁷⁶ Especially in patients with renal insufficiency, an accumulation of M3G might reveal some insights about any action or side-effects of this morphine metabolite. In a first human study, M3G administered i.v. in a dose of 30.6 mg per 70 kg did not show any

significant activity and no antagonism of analgesic or respiratory depressant effects of morphine or M6G was observed.⁵⁷

Limitations and conclusions

Clearly, a limitation of our calculation is the lack of human brain concentration data of morphine and its metabolites. We therefore used the concentration of the substances in the CSF under the notion that there might be equilibrium between CSF and the brain tissue itself. Also, most of the pharmacokinetic data of morphine and its metabolites are from studies after single-dose administration. This is clearly very different from the therapeutic situation where patients receive opioids regularly according to an individual dosing scheme for long-term pain therapy. The major strength of our calculation, however, is the strong support of the earlier proposed importance of the active M6G by applying basic clinical pharmacology methods.

In conclusion, when administering morphine to patients, the main contribution to the analgesic effect is caused by **M6G which is the dominating compound irrespective of the route of administration. Hence, most importantly, the dose of morphine has to be adjusted to the patient's kidney function.**

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Authors' contributions

Both authors contributed to every aspect of the study including writing of the manuscript.

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Declaration of interest

None declared.

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