The bioavailability and pharmacokinetics of subcutaneous, nebulized and oral morphine-6-glucuronide

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Aims Morphine-6-glucuronide (M6G), one of the active metabolites of morphine, has attracted considerable interest as a potent opioid analgesic with an apparently superior therapeutic index. To date studies have used the intravenous route, which is generally unacceptable in the treatment of cancer related pain. The aim of this study was to define the pharmacokinetics, toxicity and cardio-respiratory effects of three alternative routes of administration of M6G.

Methods Ten healthy volunteers participated in an open randomized study. Subjects received M6G 2 mg as an intravenous bolus, 20 mg orally, 2 mg subcutaneously and 4 mg by the nebulized route. Pulse, blood pressure, respiratory rate and peak flow rate were monitored and subjective toxicity recorded on rating and visual analogue scales.

Results After i.v. M6G the mean ($\pm$s.d.) AUC$(0,\infty)$ standardized to a dose of 1 mg was 223 ± 57 nmol l^{-1} h, mean elimination half-life was 1.7 ± 0.7 h and the mean clearance was 157 ± 46 ml min^{-1}. These parameters were virtually identical after subcutaneous administration which had a bioavailability ($F(0,\infty)$) of $102 \pm 35\%$ (90% CI 82, 117%) and t_{max} of 0.5 ± 0.2 h. The mean bioavailability of nebulized M6G was $6 \pm 2\%$ (90% CI 4, 7%) with a t_{max} of 1.2 ± 0.8 h. Following oral M6G two plasma M6G peaks were seen in 7 of the 10 subjects, the first with a t_{max} of 3.1 (± 0.9) h. The second peak had a t_{max} of 13.4 (± 5.0) h, started approximately 4 h after dosing, and was associated with the detection of plasma M3G and morphine, suggesting that M6G was significantly hydrolysed in the gut to morphine, which was then glucuronidated following absorption. Although the overall mean bioavailability was $11 \pm 3\%$ (90% CI 9, 12%), confining the analysis to data from the first peak suggested a bioavailability of directly absorbed M6G of only $4 \pm 4\%$. Apart from a characteristic dysphoria following intravenous and subcutaneous M6G, there was no significant toxicity.

Conclusions With the minimal toxicity reported in this and previous studies, subcutaneous infusion of M6G may potentially provide clinically useful analgesia for advanced cancer pain. Nebulized M6G is not significantly absorbed via the lungs, and if opiates are shown to have a local effect in the lung, reducing the sensation of breathlessness, then nebulized administration is likely to minimize systemic effects. Oral M6G has poor bioavailability, but is significantly hydrolysed in the gut to morphine, which is subsequently glucuronidated following absorption. This circuitous route accounts for the majority of systemically available M6G after oral administration.

Keywords: bioavailability, morphine-6-glucuronide, morphine, pharmacokinetics

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Received 3 March 2000, accepted 29 October 2001.

Introduction

Morphine is the most commonly used analgesic for severe pain. It was isolated in 1805, but information about its metabolism and the importance of its metabolites has only emerged since the late 1960s [1]. In man morphine is predominantly metabolized by hepatic glucuronidation

with the addition of the sugar molecule at the phenolic 3-hydroxyl or the alcoholic 6-hydroxyl position on the phenanthrene ring [2].

In animal models morphine-6-glucuronide (M6G) produced potent and long-lasting analgesia [3, 4], although after morphine administration the metabolite was present in low amounts in small mammals [5]. Following intravenous (i.v.) morphine administration in man morphine-3-glucuronide (M3G) is the major metabolite accounting for approximately 75% of the total area under the concentration-time curve (AUC) of morphine and its principle metabolites [6]. The next most abundant metabolite, contributing 15% of the AUC, is M6G. However, a new and specific h.p.l.c. method showed that following i.v. morphine in man M6G was present in higher concentrations than morphine from 1 h onward [6, 7] and was implicated in the narcosis seen in patients with renal failure who retained the metabolite [8]. Osborne *et al*. first reported the efficacy of M6G in man in a phase I study of i.v. M6G in patients with cancer related pain [9]. Seventeen of 19 assessable patients had useful analgesia lasting between 2 and 24 h [10]. Subsequently two studies have demonstrated that i.v. M6G is more potent than morphine with dramatically fewer side-effects, producing virtually no nausea or sedation and significantly less respiratory depression [11, 12]. In contrast recent reports have described a lack of analgesic activity of i.v. M6G in volunteers using an experimental pain model involving stimulation of nasal nociceptors with gaseous carbon dioxide [13], and no difference between preemptive M6G or placebo in a limb surgery setting [14].

M6G has been shown to possess significant μ_1-opioid receptor affinity. Its lesser toxicity may be a result of lower affinity for the μ_2-opioid receptor, thought to mediate respiratory depression and nausea [15, 16]. Recent evidence suggests that nebulized M6G may be effective in relieving breathlessness [17] although it is still uncertain whether such actions are mediated locally or via central mechanisms. The vast majority of treatment for chronic pain with morphine utilizes the oral route, while subcutaneous infusion is convenient in patients unable to take medication by mouth [18]. Therefore, the pharmacokinetics of these three alternative routes of administration of M6G have been investigated and compared with that after i.v. administration.

Methods

The study was approved by the Royal Hospital's Trust Research Ethics Committee. The preclinical toxicity and stability data for M6G have been reported in a previous study [10]. This study utilized M6G from the same batch, synthesized according to the method of Yoshimura *et al*. [19] by UFC Pharma, Manchester. Drug was made up in saline at a concentration of 1 mg ml^{-1}, sterilized by filtration, and stored under nitrogen in glass ampoules. Purity of the M6G formulation was investigated by h.p.l.c. analysis at the start and completion of the study. In addition to M6G a peak believed to be the 6-α glucuronide epimer was observed. This peak was $<1\%$ of the M6G peak height at the start of the study and $<2\%$ at completion.

Subjects and treatment

Eligibility criteria for subjects were proscribed by the Ethics committee in view of the fact that M6G is a potentially addictive substance. Volunteers could receive no more than six lifetime administrations, each at least 1 week apart. Students, preregistration house staff and secretarial staff were excluded and no undue pressure was brought to recruit subjects, who were only reimbursed reasonable expenses. All potential subjects were screened by a confidential interview with a consultant clinical pharmacologist and a specimen of urine was screened for drugs of abuse, with informed consent. Health screening consisted of a health questionnaire, clinical examination, full blood count, electrolytes and liver biochemistry, urinalysis, peak expiratory flow rate and electrocardiogram. Subjects gave informed written consent and their general practitioner was informed of their involvement by letter.

Ten healthy volunteers each received; 2 mg intravenous (i.v.) M6G in 20 ml normal saline given over 2 min, 2 mg subcutaneous (s.c.) M6G in 2 ml normal saline given as a bolus, 20 mg of oral (p.o.) M6G as a 50 ml solution in water, and 4 mg M6G nebulized in 4 ml of normal saline, via an Acorn nebuliser driven by 8 l min^{-1} air for 15 min. Doses were given in random order at least 1 week apart. One subject received an i.v. dose of 1 mg M6G after reporting the dysphoric effect of the s.c. dose to be unpleasant. Based on a previous study which suggested linear pharmacokinetics between 1 mg, 2 mg and 4 mg i.v. M6G (median $AUC(0,\infty)$ values 349, 665 and 1176 nmol l^{-1} h, respectively) [9], measured plasma M6G concentrations were corrected to a 2 mg dose in this subject. Subjects were fasted overnight prior to drug administration, were nil-by-mouth for the first 4 h of the study and remained supine for the first 2 h of the study.

Assessments

Heart rate and blood pressure were recorded by a DYNOMAP automatic sphygmomanometer at 0, 0.5, 1 and 2 h. Peak expiratory flow rate (PEFR) was recorded

prior to and 30 min after the administration of M6G as the mean of three forced expirations and to the nearest 5 l min^{-1}. Toxicity was recorded at 0, 0.25, 0.5, 1, 2, 4, 6, 8, 12 and 24 h using visual analogue (scale 0–100 mm) [20] and Modified Borg Scales (scale 0–10) [21]. The latter was used because of greater sensitivity in reporting milder symptoms. Subjects were specifically asked about nausea, sedation and mood and asked to comment on any other symptoms so as not to prejudice possible responses. Dysphoria was therefore only recorded on the Borg scale. On each occasion a new scale was presented and comparison with earlier responses was not permitted. All observations were made by one of the authors (RP).

Pharmacokinetic analysis

Blood samples (6 ml) were taken prior to and during the 24 h after drug administration at time 0, 2, 5 and 10 min and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12 and 24 h. Plasma was separated by centrifugation at 1200 *g* for 10 min and stored at -40° C prior to assay. Morphine, M6G and M3G were quantified by reversed phase ion paired h.p.l.c. analysis using a previously published method [22], but with a solid phase extraction device (ASPEC, Anachem, Luton Beds) and Varian 100 mg C_8 cartridges (Anachem, Luton, Beds). Briefly, cartridges were primed with methanol (1.5 ml), 10 mM sodium di-hydrogen phosphate, pH 2.1, containing 10% acetonitrile (1.0 ml), and de-ionized water (1.5 ml). Plasma (600 μl) buffered with 500 mM ammonium sulphate pH 9.3 (1800 μl) was then applied to the cartridge, and after washing with 5 mM ammonium sulphate, pH 9.3 (6 ml) and de-ionized water (200 μl) compounds of interest were eluted with 10 mM sodium di-hydrogen phosphate, pH 2.1, containing 10% acetonitrile (800 μl). H.p.l.c. analysis was as described [22], with detection of resolved components by electrochemical detection (+0.35 V) for morphine and morphine-6-glucuronide and fluorescence detection for morphine-3-glucuronide (λ_{Ex} 210 nm, $\lambda_{Em} > 300$ nm). Limits of sensitivity were 2 nmol l^{-1} for morphine and M6G and 20 nmol l^{-1} for M3G. Between assay variability was $<12\%$ at morphine and M6G concentrations of 20, 80 and 350 nmol l^{-1} and $<14\%$ at M3G concentrations of 200, 3500 and 8000 nmol l^{-1}. High plasma concentrations of M3G do not interfere with the determination of M6G or morphine.

Pharmacokinetic analysis was undertaken using Kinetica 2000 version 3.0 (Innaphase Corp, Philadelphia, PA, USA) using noncompartmental methods. Area under the concentration-time curve (AUC) was calculated using the trapezoidal method by calculating the linear areas of adjacent data points to t_{max}, and the logarithmic area from the exponential fit of adjacent data points to t_n. Area under the moment curve (AUMC) was calculated from the product of concentration and time at each data point. AUC and AUMC were extrapolated to infinity using the concentration at t_n and the elimination rate constant (k_{el}), derived using those data points giving the best fit (minimal residual error) by log-linear regression of the terminal exponential phase (between 4 and 11 data points). The elimination half-life ($t_{1/2}$) was calculated as 0.693 divided by the elimination rate constant (k_{el}). The mean residence time (MRT) was calculated as AUMC/AUC after i.v., s.c. and oral dosing, and as AUMC/AUC − dosing time/2 for nebulized administration. Clearance (CL) was calculated as dose divided by AUC$(0,\infty)$ and volume of distribution at steady state (Vd_{SS}) as the product of CL and MRT. Deconvolution analysis was performed within Kinetica using a model independent method (numerical deconvolution) to analyse absorption profiles. The results of this analysis are presented as percentage of dose absorbed against time.

For bioavailability estimates the mean and 90% confidence interval of the difference between the log-transformed AUC values is presented.

Statistical investigations were performed in Minitab ver 13 (State College, Ohio, USA). Tests for normality were carried out using the Ryan Joiner test. Within subject comparisons between different routes of administration were performed using 1- or 2-way analysis of variance if normally distributed and Kruskall-Wallis or Friedman's tests if not normally distributed. Where these analyses indicated a difference between treatments, individual comparisons were made using paired *t*-tests or Wilcoxon signed ranks matched pairs tests for normally or non normally distributed data, respectively.

Results

Demographic details

The 10 volunteers had a mean (range) age of 31 (24–42) years, weight of 71 (55–88) kg, serum creatinine of 89 (71–100) mmol l^{-1} and estimated GFR [23] of 109 (72–133) ml min^{-1}. Four were female and used adequate contraception for the duration of the study.

Pharmacokinetic parameters

Mean (±s.d.) pharmacokinetic parameters are recorded in Table 1. On one of the study days in each of two subjects problems with the venous cannula meant that there were insufficient numbers of samples for pharmacokinetic analysis.

Table 1 Mean (±s.d.) pharmacokinetic parameters for M6G after intravenous, subcutaneous, nebulized and oral administration. It was not possible to derive elimination half-life after oral M6G, and MRT, AUC(0,∞) corrected to 1 mg and bioavailibility have been derived using AUC(0,t_n) values. Statistical differences between dose independent or dose corrected parameters have been investigated by paired *t*-test, except t_{max} and MRT where Wilcoxon signed ranks matched pairs test was used.

Route and dose	*i.v. 2 mg*	*s.c. 2 mg*	*Nebulized 4 mg*	*p.o. 20 mg*
n	10	9	9	10
Elimination $t_{1/2}$ (h)	1.7±0.7	1.9±0.4	3.1±1.1**	–
Clearance (ml min^{-1})	157±46	154±24	–	–
Vd_{SS} (l)	16.2±4.4	20.5±3.3	–	–
C_{max} (nmol l^{-1})	539±279	207±51	11±5	42±28
t_{max} (h)	0.1±0.1	0.5±0.2**	1.2±0.8**	6.7±4.3**
AUC(0,t_n) (nmol l^{-1} h)	445±115	431±72	43±19	457±113
AUC(0,∞) (nmol l^{-1} h)	458±117	444±73	53±19	–
AUMC(0,t_n)				5106±1379
AUMC(0,∞)	836±351	1001±242	268±133	
MRT	1.8±0.5	2.2±0.3**	4.9±1.1**	11.5±2.7**,‡
AUC(0,∞) (nmol l^{-1} h) corrected to a dose of 1 mg	223±57	222±37	11±5***	23±6***,‡
Bioavailability F(0,∞) (%)	(100)	102±35	6±2	11±3‡
90% CI		82–117	4–7	9–12‡

*$P<0.05$, **$P<0.01$, ***$P<0.001$ compared with i.v. M6G.
‡Calculated using AUC(0,t_n).

Mean plasma concentrations after each route of administration are shown in Figure 1. The elimination $t_{1/2}$ of M6G after i.v. dosing was 1.7±0.7 h, with a CL of 157±46 ml min^{-1}, and Vd_{SS} of 16.2±4.4 l. A summary of the pharmacokinetic parameters after each route of M6G administration is given in Table 1.

Plasma M6G concentrations after s.c. M6G were similar to those after i.v. administration from 0.5 h onwards (Figure 1). The elimination $t_{1/2}$ after s.c. dosing was 1.9±0.4 h, with a CL of 154±24 ml min^{-1} and bioavailability of 102±35% (range 70–188%, 90% CI 82, 117%). The subject with the very high bioavailability (188%) had a low AUC(0,∞) (260 nmol l^{-1} h) and high CL (258 ml min^{-1}) after i.v. dosing. For the remaining nine subjects the bioavailability ranged from 70 to 140%. Absorption from the site of administration was rapid, as shown in Figure 2, and for most subjects the absorption profile had plateaud by around 1 h. The subject who reported unpleasant dysphoric effects at 2 mg s.c. M6G did not have a markedly different M6G AUC(0,∞) (386 nmol l^{-1} h) or CL (173 ml min^{-1}) compared with other subjects.

Following 15 min nebulized M6G, plasma concentrations rose slowly to peak at around 1.2±0.8 h, with an AUC(0,∞) of 53±19 nmol l^{-1} h and $t_{1/2}$ of 3.1±1.1 h. This elimination half-life was significantly longer than after i.v. M6G ($P=0.002$), possibly reflecting the continued, prolonged absorption suggested by the deconvolution analysis (Figure 3). The mean bioavailability (F(0,∞)) of nebulized M6G was 6±2% (range 4–11%, 90% CI 4, 7%). No morphine or M3G was detected after s.c. or nebulized M6G.

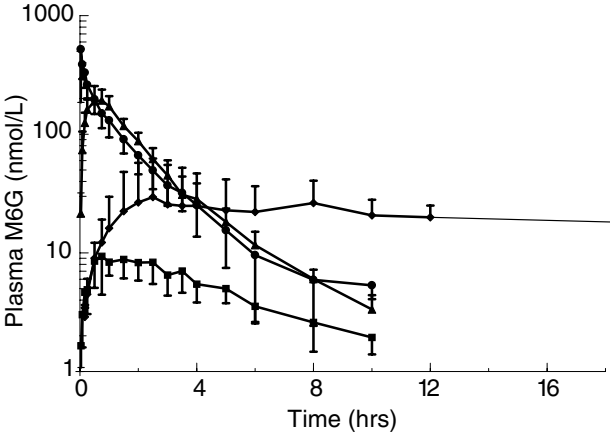

Figure 1 Mean (+s.d.) measured M6G plasma concentrations after intravenous (2 mg, ●), subcutaneous (2 mg, ▲), nebulized (4 mg, ■) and oral (20 mg, ◆) M6G administration.

Following oral M6G, two plasma M6G peaks were seen, resulting in an apparent plateau in the mean plasma concentration as illustrated in Figure 4. The first peak had a mean t_{max} of 3.1±0.9 h, while the second larger peak typically started around 4 h after dosing and had a mean t_{max} of 13.4±5.0 h. This second peak was accompanied by the presence of plasma morphine and/or M3G in all but three subjects (subjects 2, 4 and 9). M6G was detected in the plasma of nine subjects at 24 h, with a mean concentration of 17±6 nmol l^{-1}. Plasma M6G was not detected beyond 10 h in subject 2. The mean overall C_{max} was 42±28 nmol l^{-1}, with a C_{max} for the first and second plasma M6G peak of 32±33, and

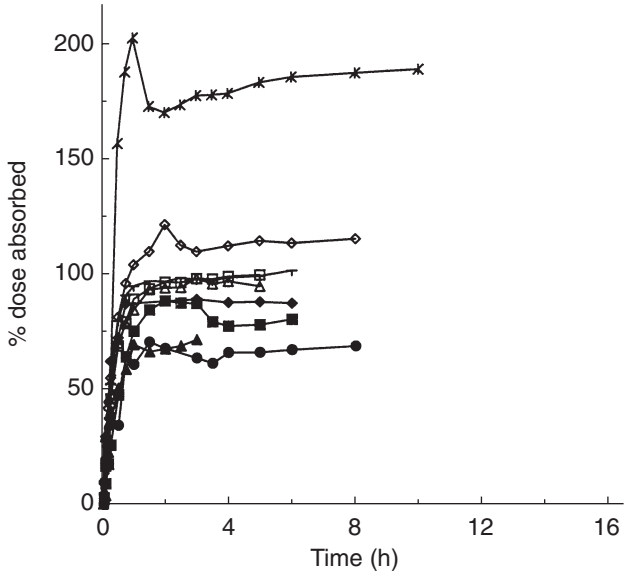

Figure 2 Percentage dose absorbed against time for individual subjects after 2 mg subcutaneous M6G given as a bolus in 2 ml normal saline.

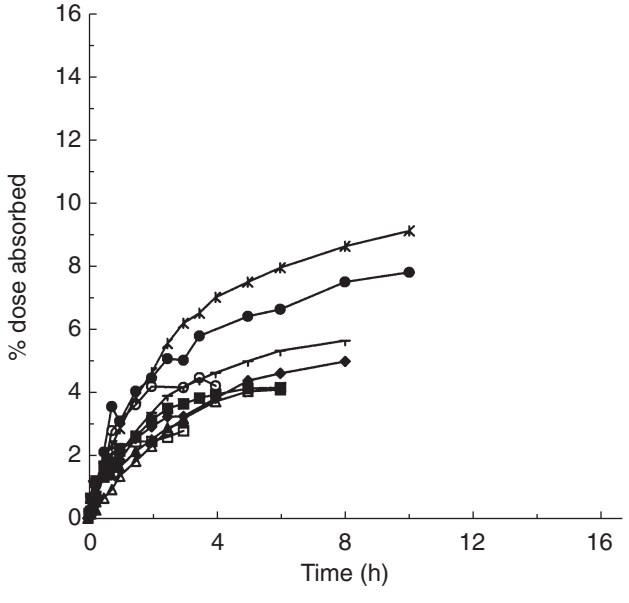

Figure 3 Percentage dose absorbed against time for individual subjects after 4 mg nebulized M6G administered over 15 min in 4 ml normal saline.

30 ± 11 nmol l^{-1}, respectively. The protracted and often biphasic absorption of M6G after oral dosing in most subjects is clearly seen in the absorption profile shown in Figure 5. Because of this prolonged absorption it was not possible to derive reliable estimates of elimination half life after oral dosing. The mean AUC$(0,t_n)$ for oral M6G was 457 ± 113 nmol l^{-1} h, with the mean AUC of the first peak (0–4 h), extrapolated to infinity using the elimination $t_{1/2}$ of i.v. M6G for each subject, being

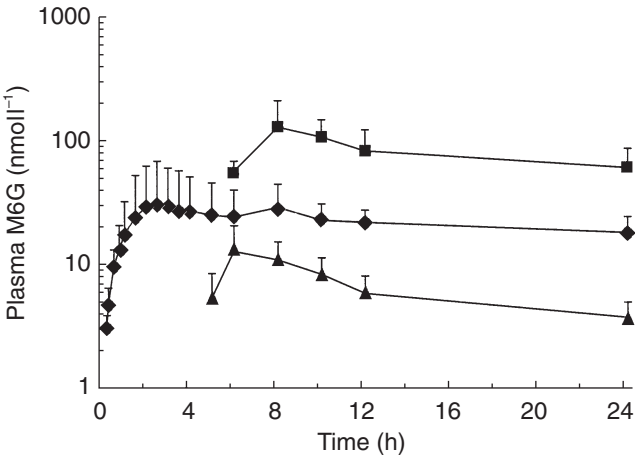

Figure 4 Mean (+s.d.) measured M6G, M3G and morphine concentrations after 20 mg oral M6G. ■ M3G, ◆ M6G, ▲ morphine.

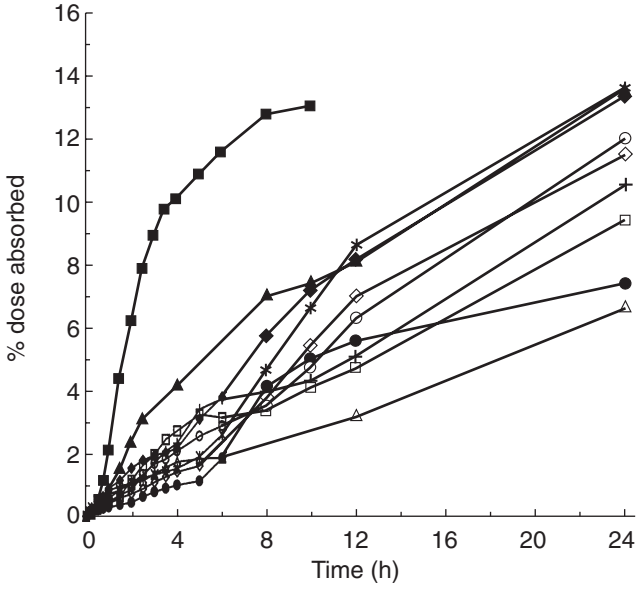

Figure 5 Percentage dose absorbed against time for individual subjects after 20 mg oral M6G given in 50 ml water.

85 ± 87 nmol l^{-1} h. The overall bioavailability of oral M6G (using AUC$(0,t_n)$) was $11 \pm 3\%$ (range 6–15%, 90% CI 9, 12%, highest value again in subject with highest i.v. M6G clearance). However, the bioavailability of directly absorbed oral M6G, that contributing to the first plasma M6G peak up to the appearance of morphine or M3G, was only $4 \pm 4\%$ (range 1–12%). In most subjects plasma M6G appeared to be rising at 24 h, as shown in the absorption profiles (Figure 5), and it is likely that the derived bioavailability using AUC$(0,t_n)$ is an underestimate of the true bioavailability.

The correlation between estimated glomerular filtration, as calculated by the Cockcroft & Gault formula [23] and the M6G clearance for i.v. dosing was $r = 0.04$

Table 2 Mean (range) toxicity scores following i.v., s.c., nebulized and oral M6G. Treatments were compared using Friedmans nonparametric analysis of variance and where indicated ($P<0.05$ for treatment) each route was compared with i.v. M6G by Wilcoxon signed ranks matched pairs test.

	i.v.	*s.c.*	*Nebulized*	*Oral*
Nausea				
Max Borg score	2.0 (0–5)	0.25 (0–4)	0.0 (0–3)	0.0 (0–2)
Max change in VAS (mm)	10 (0–57)	13 (0–38)	3 (1–24)	10 (0–20)
Sedation				
Max Borg score	3.0 (0.5–4)	1.25 (0–4)	0.5 (0–3)	0.5 (0–4)
Max change in VAS (mm)	18 (0–72)	10 (0–41)	4 (0–37)	7 (0–37)
Mood				
Max Borg score	1.0 (0–4)	1.25 (0–3)	0.5 (0–2)	0.0 (0–2)
Max change in VAS (mm)	9 (0–62)	6 (0–37)	3 (0–29)	4 (0–24)
Dysphoria				
Max Borg score	3.0 (2–9)	3.0 (0–4)	1.25 (0–3)⋆	1.25 (0–3)⋆

⋆$P<0.05$.

for all subjects, $r=0.44$ when the subject with the very high M6G clearance was excluded, and $r=0.54$ for s.c. dosing.

Pharmacodynamic parameters

Toxicity is summarized in Table 2. The administration of M6G was associated with little toxicity, although following i.v. and s.c. dosing dysphoria was reported in 9 of the 10 subjects, typically described as a tightness that started in the neck and chest and which was subsequently associated with a feeling of heaviness in the limbs. This sensation typically lasted for less than 10 min and was intense for only 2 min. Its onset and intensity was similar after both i.v. and s.c. administration, four subjects felt that the effect lasted longer after s.c. M6G and two reported the reverse. By Kruskal–Wallis analysis the ratings of the dysphoria from M6G by these two routes showed no significant difference. The median dysphoria score after both i.v. and s.c. M6G was three, which is 'moderate' on the Borg scale. Dysphoria scores for oral ($P=0.02$) and nebulized ($P=0.04$) M6G were significantly lower than for i.v. M6G.

There was virtually no toxicity after oral and nebulized M6G. Most subjects complained of hunger and caffeine withdrawal. No subject vomited or required antiemetics.

Blood pressure varied less than 10% with no significant pattern and pulse slowed by a mean ($\pm$s.d.) of 16 ($\pm$9), 12 ($\pm$10), 7 ($\pm$13) and 14 ($\pm$9) beats min^{-1} at 1 h for i.v., s.c., oral and nebulized routes, respectively (NS). The mean ($\pm$s.d.) changes in PEFR were -9 ($\pm$13), -5 ($\pm$14), 2 ($\pm$15), and -7 ($\pm$34), respectively (NS).

Discussion

This study documents the pharmacokinetic parameters of M6G, administered by the i.v., s.c., nebulized and oral routes in normal volunteers. Three clear conclusions can be drawn. Firstly, the bioavailability and distribution time of s.c. M6G suggest that this route may be suitable for patients with severe pain requiring rapid analgesia, or in those who are unable to take oral medication. Secondly, the systemic bioavailability of nebulized M6G is low, minimizing toxicity if a peripheral effect on breathlessness from inhalation is confirmed. Lastly, the unexpected enteric hydrolysis of oral M6G to morphine and subsequent absorption and re-glucuronidation argues against the use of oral M6G to maintain systemic M6G concentration, which can be achieved with oral morphine per se.

The pharmacokinetic parameters for M6G after i.v. administration are within the ranges of previously published data for normal volunteers [24, 25]. Hanna reported pharmacokinetic analysis of M6G in six volunteers at doses of 30 $\mu g\ kg^{-1}$ and 60 $\mu g\ kg^{-1}$, with a normalized AUC$(0,\infty)$ of 223 ± 25 nmol l^{-1} h/mg dose, and clearance of 158 ± 37 ml min^{-1}. The elimination $t_{1/2}$ was 1.9 ± 1.0 h, similar to that of metabolically produced M6G of 2.6 ± 0.7 h [6]. Lotsch *et al.* studied 20 healthy male subjects who received 1.5, 3.0 and 4.5 mg/70 kg M6G by a combination of bolus M6G (2/3 of the total dose) followed by a 4 h infusion [24]. The mean elimination half-life was 1.4 ± 0.4 h and clearance 153 ± 28 ml min^{-1}/70 kg. In cancer patients the normalized M6G AUC$(0,\infty)$ was 390 ± 263 nmol l^{-1} h/mg dose, M6G clearance was 96 ± 38 ml min^{-1}, and elimination $t_{1/2}$ 3.2 ± 1.6 h [10]. The decreased M6G clearance in this group is most likely explained by poorer renal function, as M6G is retained in the presence of renal failure [8], and when a wide variation of renal function exists a strong correlation between M6G clearance and creatinine clearance can be demonstrated [10].

Comparing the M6G AUC after i.v. and s.c. dosing suggests that M6G administered by the s.c. route is

completely bioavailable. This route is commonly used to administer morphine for break-through pain in cancer patients [18]. Subcutaneous M6G appears to be absorbed into the systemic circulation relatively quickly from a small depot with a t_{max} of 0.5 ± 0.2 h. This suggests that the endothelium, without a basement membrane, facilitates passage of this large and polar molecule, to the capillary and post capillary blood. Nebulized M6G, with a t_{max} of 1.2 ± 0.8 h, has a much slower passage into the circulation despite a much larger surface area, suggesting a significant delay at the basement membrane. The low bioavailability of nebulized M6G, despite the <5 μm particle size produced by the nebuliser system used [26], would preclude this route as a means of delivering the drug as an analgesic. An unquantified, although probably large, amount of drug will have been retained in the nebuliser, lost to the atmosphere or swallowed. The significantly longer elimination $t_{1/2}$ after nebulized M6G suggests that there may be protracted absorption from the lungs, buccal mucosa, or possibly the gut. Mitigating against the latter possibility is the absorption profile of nebulized M6G (Figure 3), which is somewhat different from that of oral M6G (Figure 5), and the absence of plasma morphine or M3G after nebulized M6G in any subject, albeit at a lower dose than with oral M6G where these compounds were detected.

Anecdotal reports of the efficacy of nebulized opioids have fuelled the investigation of this route for morphine in breathless patients, although studies have failed to show any improvement with nebulized morphine [27]. In a placebo controlled study of nebulized morphine (12.5 mg) and M6G (4 mg) in patients with stable chronic obstructive pulmonary disease, a significantly superior improvement in exercise duration with M6G ($P<0.01$) was found, suggesting a particular role for the metabolite [17]. Although it has long been assumed that cough and breathlessness are mediated centrally [28], recent data suggests that opioid receptors are present in the lung [29], although exhibiting nonconventional binding [30, 31]. If opiates are shown to have a local effect in the lung then nebulized M6G administration is likely to minimize any systemic toxicity whilst exposing pulmonary, or bronchial, receptors to a potent μ-agonist for prolonged periods.

Outside the postoperative setting the majority of strong analgesics are given by mouth, for convenience [18]. Our data suggest that in most subjects the bioavailability of directly absorbed M6G after oral administration is very low, and that oral M6G is significantly hydrolysed in the gut to morphine, which is absorbed and subsequently re-glucuronidated. It remains unclear why this hydrolysis to morphine was not seen in all subjects. A recent study investigating M6G intestinal absorption in rats reported limited hydrolysis to morphine in the small intestine, but much higher hydrolysis in the colon, with a prolonged absorption profile that was attributed to enterohepatic re-circulation [32]. In our own study there was little evidence of such late re-circulation after intravenous or subcutaneous dosing, suggesting that the sustained plasma M6G seen after oral dosing in most subjects was due to hydrolysis of M6G to morphine in the gut, with re-conversion to M6G, and M3G, after morphine absorption. Indeed the ratio of M3G : M6G from 6 to 8 h onwards in these subjects (3.5 : 1) was similar to the M3G : M6G AUC ratio seen after the administration of oral morphine in normal volunteers (5.9 : 1). Furthermore, plasma M3G and M6G concentrations plateau in patients with renal failure, suggesting that there is no other significant route for clearance other than renal elimination [8].

No morphine, M3G or nor-morphine was found after i.v., s.c. or nebulized M6G. Boerner *et al.* hypothesized that the di-glucuronide would be produced as a further metabolite [6]. However, this metabolite has not been found [33], and it is probable that significant stearic hindrance prevents the formation of such a bulky, hydrophilic molecule.

The toxicity of this potent analgesic was minimal by any route. This supports the conclusion of prior studies [10–12, 24] and is in keeping with the observation that M6G has less affinity for the μ_2, or toxicity receptor [15, 16]. Recent work has suggested that its actions may be specifically mediated through a third μ-receptor isotype the 'M6G-receptor' produced by post-translational splicing of MOR-1 mRNA [34].

In summary this study represents the first report of the administration of M6G by the s.c., nebulized and oral routes in man. With the exception of C_{max}, M6G pharmacokinetics after i.v. and s.c. dosing are similar. Nebulized M6G is poorly absorbed, and the previously reported pharmacodynamic effects of M6G administered by this route may therefore be mediated locally rather than centrally. Absorption of oral M6G is also low, but in most subjects is associated with the appearance of plasma morphine and M3G, probably due to hydrolysis to morphine in the gut. The derived 'bioavailability' of M6G following oral morphine has been reported as 14% [3] and 11% [35]. This is similar, and possibly higher, than the bioavailability reported here for orally administered M6G of 11 (± 3)%. Oral M6G, in comparison with oral morphine, appears, paradoxically, to be an inefficient way to deliver M6G, particularly with the accumulation of M6G with chronic dosing of morphine [36].

These results encourage further investigation of a possible local effect of nebulized M6G in the lung in the relief of breathlessness, and the use of s.c. M6G as an analgesic.

The study was supported by the Imperial Cancer Research Fund.

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