ORIGINAL ARTICLE

Morphine analgesia in cancer pain: Role of the glucuronides

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ABSTRACT

Preclinical data and limited studies in humans have suggested that morphine-6-glucuronide (M6G) has analgesic activity and morphine-3-glucuronide (M3G), contributes adversely to the therapeutic effect of morphine. This open point-prevalence study in 103 patients on oral morphine for cancer-related pain investigated the correlations between morphine doses, metabolites, and the degree of pain relief or toxicity. Morphine, M6G, and M3G were assayed by high-performance liquid chromatography on a single blood sample taken between two and four hours after dose. Pain, analgesia, and toxicity were recorded on numerical and visual analog scales. Patients received a median dose of 60 (range, 10 to 620) mg per day morphine, for a median of 4.1 weeks (range, 0.2 to 46.0 weeks). M3G:M6G ratios fell within a narrow range, with a median value of 4.39 (interquartile range, 3.78 to 6.96; range, 2.18 to 14.95). There were no significant correlations between M3G:M6G and morphine dose, or any measure of analgesia. The correlation between plasma concentration and pain score (i.e., better analgesia) was stronger for M6G ($r = 0.308$, $p < 0.01$) than morphine ($r = 0.197$, $p = 0.05$). These data suggest that M6G contributes significantly to the analgesic potency of oral morphine. No evidence was found for differences in M3G:M6G ratios contributing to analgesia or toxicity.

Key words: morphine, cancer pain, glucuronides, analgesia

INTRODUCTION

Morphine remains a mainstay of treatment for patients with severe cancer-related pain.[1] Although the recommendation is to titrate dose against effect, either analgesia or toxicity, this is empirical advice, and attempts to predict effective doses or respond to inadequate plasma concentrations of analgesics have generally proved fruitless.[2]

Oral morphine undergoes extensive presystemic glucuronidation, predominantly in the liver, to morphine-3-glucuronide (M3G) (80 percent) and morphine-6-glucuronide (M6G) (15 percent), with morphine contributing less than 5 percent of the total area under the concentration time curve (AUC).[3] In animal models, M6G gives potent and long-lasting analgesia.[4,5] Initially, M6G was thought to be present in only small amounts in humans, as in the rat.[6] However, the development of a new and specific high-performance liquid chromatography (HPLC) method revealed that M6G was present in higher concentrations than morphine after administration of intravenous (IV) morphine from one hour onward. Indeed, after oral morphine, M6G was found in considerably larger amounts at all time points, consistent with first-pass metabolism.[3,7] The first suggestion of M6G activity in humans was the observation of protracted narcosis in patients with renal failure who metabolize morphine yet retain the glucuronides.[8] M6G's actions have recently been confirmed in human studies, demonstrating that IV M6G is more potent than morphine with fewer side effects, producing little nausea or sedation and significantly less respiratory depression.[9-13]

Experiments in μ-opioid receptor gene knockout mice suggest that M6G acts predominantly through this receptor.[14] M6G has significantly greater analgesic potency than morphine,[4,12] such that some authors have claimed that it contributes up to 85 percent of the analgesic efficacy of morphine.[15,16] Others have argued that the effects of M6G may only be apparent with chronic dosing because of poor penetration to the central nervous system.[17] Modeling of effect-site concentrations of M6G suggests that after multiple oral doses of morphine, M6G might reach concentrations two times greater than that of morphine in the brain.[18]

Although M3G has no analgesic activity, it has been suggested that it may functionally antagonize the effects of morphine in rats.[19,20] Furthermore, other investigators have claimed that abnormal metabolite ratios may explain

4	3	2	1	0
No pain	Slight pain	Moderate pain	Severe pain	Very severe pain

Figure 1. Pain score.

the variation in the analgesic potency of morphine,[21] and that morphine tolerance may owe to accumulation of M3G over time.[22] These results have not been consistently reproduced in preclinical studies and there has been skepticism about this apparent activity.[23,24] There is an obvious analogy, however, to the accumulation of the neurostimulatory metabolite of meperidine; normeperidine,[25] hyperalgesia, and myoclonus have been attributed to M3G[26], and worse pain relief and increased toxicity has been reported to result from a disproportionately high M3G concentration.[22]

In this point-prevalence study, we sought to quantify the influence of plasma concentrations and ratios of morphine and its principal glucuronide metabolites on the analgesic and unwanted effects of oral morphine and to investigate the incidence of paradoxical pain and/or abnormally raised M3G:M6G ratios.

MATERIALS AND METHODS

The study was approved by the Royal Hospitals Trust Research Ethics Committee and was undertaken in the Department of Medical Oncology at St. Bartholomew's Hospital.

Patients

Patients with chronic severe pain related to cancer and receiving oral morphine were eligible for the study and gave informed consent. Patients were in- or outpatients within the Solid Tumour Division of the Department of Medical Oncology. Patients with neuropathic pain, typically much less responsive to opiates, were not excluded. Patients deemed at the multidisciplinary meeting to be "imminently dying" were excluded.

Assessment

A single 6-mL blood sample was drawn into a lithium heparin tube between two and four hours after taking oral morphine. This interval was chosen to avoid the first hour in which the glucuronide:morphine ratios are changing.[3] After centrifugation the plasma was separated and stored at -40°C until analysis. Plasma morphine, M3G, and M6G were quantitated by reversed-phase ion-paired high-performance liquid chromatography.[27] Information about patients' pain, analgesia, and limited demographic details were recorded on a proforma from data acquired at interview by one of the investigators (RTP) or a research nurse. Further data were abstracted from the patients' notes and drug chart. Serum creatinine, bilirubin, alkaline phosphatase, and aspartate transaminase were recorded as measures of renal and hepatic function. The normal laboratory ranges were creatinine 79 to 118 μmol per L in men and 58 to 93 μmol per L in women, bilirubin < 17 μmol per L, AST < 39 IU per L, and ALP < 117 IU per L.

At the time of taking the blood sample, the patient was asked to assess the degree of pain and pain relief using validated pain assessment scales (Figures 1 and 2) and a visual analog scale (VAS).[28] It was made clear that this was to be an impression of their overall experience of pain, at that time, on morphine and the scales were scored so that higher values represented better pain relief or less pain (Figures 1 and 2). Patients were also asked about the character of the pain and how this had changed in the two weeks prior. The subjective experience of side effects was reported without a formal grading system.

Statistical analysis

The intention was to enroll at least 100 patients into the study to reliably determine the population estimates and variability in the relative plasma ratios and amounts of M3G, M6G, and morphine. As very few studies have shown any correlation between analgesia and plasma concentrations, no accurate estimate of sample size could be undertaken. The data were checked for normality of distribution and rank correlation performed, taking $r > 0.200$ and $p < 0.05$ as significant. Subset analysis was performed using the Mann-Whitney test with $p < 0.05$ considered significant. Stepwise regression analysis was used to determine the influence of organ function on analgesia, measured plasma concentration, and concentration ratios.

RESULTS

Demographics

One hundred and three patients were studied, 50 men

My pain has:

5 ( ) been completely relieved
4 ( ) been almost completely relieved
3 ( ) eased moderately
2 ( ) eased only slightly
1 ( ) not changed at all
0 ( ) become more intense

Figure 2. Pain relief.

Table 1. Summary of mean (± SD and range) dose and ratio data		
	Value	
	Plasma concentration (nmol per L)	Ratio
M3G	1,379 (± 1,662; 36 to 12,530)	
M6G	266 (± 296; 8 to 2,048)	
Morphine	59 (± 67; 2 to 424)	
M6G + morphine	333 (± 332; 19 to 2,130)	
M3G:morphine		33.0 (± 31.1; 2.8 to 80.3)
M3G:M6G		5.6 (± 2.2; 2.2 to 15.0)
M6G:morphine		6.5 (± 6.6; 0.6 to 47.4)
M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide; SD, standard deviation.		

and 53 women, with a median age of 57 (range, 22 to 88) years and weight of 65 (range, 36 to 104) kg. The most common cancers were colorectal (22 patients), non–small-cell lung cancer (10), breast cancer (10), adenocarcinoma of unknown primary (nine), small-cell lung cancer (six), and pancreatic cancer (six).

Median serum creatinine was 80 (range, 40 to 1,740) µmol per L, and was above the upper limit of normal in 10 patients. Cockcroft-Gault estimation of glomerular filtration rate (GFR) gave a median GFR of 71 (range, 4 to 140) mL per min.[29] Plasma creatinine correlated with M3G:morphine ($r = 0.518$, $p < 0.001$) and M6G:morphine ratios ($r = 0.681$, $p < 0.001$). Liver function tests were abnormal in 20 patients in whom the median values for bilirubin, alkaline phosphatase, and aspartate transaminase were 14 (range, 4 to 411), 482 (range, 173 to 2,871), and 62 (range, 10 to 196) µmol per L respectively. No association was found between liver impairment and analgesia, side effects, or plasma ratios and concentrations.

Patients were taking oral morphine at a median dose of 60 (range, 10 to 620) mg per day; a mean dose of 106 (± 121) mg. Eighty-five patients were taking MST® (Morphine Slow-Release Tablets, NAPP Laboratories, Cambridge, United Kingdom) bid, and the remainder were taking morphine solution. Patients had been on morphine for a median of 4.1 (range, two days to 46 weeks) weeks; a mean of 8.5 (± 10.9) weeks. Twenty-five patients had been on morphine for less than two weeks. The blood was collected within one hour of the last dose of morphine in four patients. Dose correlated with the length of time on morphine ($r = 0.40$, $p < 0.01$).

Seventy-five patients (74 percent) were taking coanalgesics. Forty-seven (46 percent) were on nonsteroidal anti-inflammatory agents (NSAIDs), 13 (13 percent) on benzodiazepines, 11 (11 percent) on tricyclic antidepressants, and four (4 percent) on anticonvulsants. Patients on NSAIDs may have had more side effects ($r = 0.266$, $p = 0.06$), and the prescription of antiepileptics ($r = 0.23$, $p = 0.07$), but not antidepressants ($r = 0.08$), was associated with poorer pain relief. Use of tricyclics was associated with a slightly higher plasma morphine concentration, although the association did not achieve statistical significance ($r = 0.19$). The dose of morphine taken by patients receiving tricyclic antidepressants [160 (± 151) mg per 24 hours] appeared to be greater than for those not taking tricyclic antidepressants [98 (± 115) mg per 24 hours].

Plasma concentrations and ratios

Mean plasma concentrations and ratios are summarized in Table 1, and these values for ranges of daily doses are presented in Table 2. The frequency distribution of plasma concentrations of morphine + M6G is plotted in Figure 3. M6G was more highly correlated with M6G + morphine ($r = 0.98$, $p = 0.001$) than was morphine ($r = 0.57$, $p < 0.05$), reflecting the fact that M6G contributes more to the total AUC. Plasma M3G and M6G were tightly correlated ($r = 0.94$, $p < 0.001$) as were the M3G:morphine and M6G:morphine ratios ($r = 0.91$, $p < 0.001$). Dose correlated with plasma concentrations of M3G ($r = 0.30$, $p < 0.01$), M6G ($r = 0.36$, $p < 0.01$), morphine ($r = 0.40$, $p < 0.01$) and M6G + morphine ($r = 0.39$, $p < 0.01$) (Figure 4), but not with any of the ratios. The 62-fold dose range was associated with a 212-fold range for morphine, a 348-fold range for M3G, and a 256-fold range for M6G plasma concentrations.

M3G:M6G ratios were not normally or log-normally distributed. The mean (± standard deviation) M3G:M6G ratio was 5.60 (± 2.24) (Figure 5). The median value was 4.39, with the values spanning a seven-fold range of 2.18 to 14.95. The interquartile range was 3.78 to 6.96. There was no correlation between M3G:M6G ratio and duration of treatment ($p = 0.65$).

Table 2. Summary of mean (± SD) plasma concentrations (nmol per L) and ratio data for different dose levels				
	Dose (mg) per 24 h			
	0 to 50	51 to 100	101 to 200	201 to 620
n	40	30	14	15
M3G	908 (± 2,013)	1,211 (± 778)	1,811 (± 1,238)	2,710 (± 1,800)
M6G	175 (± 356)	233 (± 149)	311 (± 176)	550 (± 302)
Morphine	28 (± 26)	63 (± 55)	73 (± 74)	117 (± 111)
M3G:M6G	5.7 (± 2.3)	5.8 (± 2.7)	6.0 (± 1.8)	4.9 (± 1.6)
M3G:morphine	36.6 (± 39.3)	28.8 (± 23.7)	34.9 (± 17.9)	34.3 (± 35.1)
M6G:morphine	7.3 (± 8.8)	5.5 (± 4.9)	5.7 (± 2.6)	7.5 (± 6.5)
M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide; SD, standard deviation.				

Efficacy and toxicity

Patients appeared to accurately report their symptoms using the scales, with only one patient recording severe pain and good pain relief. Eighty-six patients (83 percent) had moderate or better pain relief, and of this group 74 percent [64 of the total group (62 percent)] had almost complete or complete pain relief. The two measures of pain, pain score and VAS, were well correlated with $r = 0.81$ ($p < 0.001$). Pain relief (PR) score correlated with pain score ($r = 0.59$, $p = 0.001$) and VAS ($r = 0.51$, $p = 0.001$). Mean pain score was 3.58 (± 1.16), between "slight" (3) and "no" (4) pain. The only measure of analgesia to correlate with any plasma concentration was the pain score, which correlated only with M6G ($r = 0.21$, $p = 0.03$) (not shown graphically), but not morphine ($r = 0.03$) or M3G ($r = 0.16$), while M6G + morphine approached significance ($r = 0.19$, $p = 0.06$). For further analysis, the data were divided into two subsets: greater than and less than the median. In subset analysis, comparing greater than and less than the median, higher values of M6G + morphine were significantly associated with pain score ($p = 0.017$) as was comparison of the highest with the lowest quartile ($p = 0.032$). In the same analysis, plasma M6G was highly significantly associated with pain score ($p = 0.008$); however, there was no association with plasma morphine concentrations ($p = 0.32$). Stepwise regression analysis failed to find any significant association between pain score and any pharmacokinetic parameter.

Seventeen patients (17 percent) had poor pain control as defined by a PR score of 2 (minimal PR) or less. Eleven patients (11 percent) had particularly severe toxicity, and only five (5 percent) of the patients had poor efficacy and excess toxicity. In this latter group, the mean M3G:M6G ratio was 4.02 (± 2.37), not significantly different from the mean M3G:M6G ratio for the 43 patients with good analgesia (pain score 3 or 4 and PR 4 or 5) and no excess toxicity of 5.62 (± 2.32) ($p = 0.498$). No atypical toxicity was reported. No myoclonus was observed. Only three patients, all with normal renal function, had significant mental obtundation.

Two patients at the time of this study had pain that appeared to be worsening because (as opposed to in spite) of morphine, referred to as paradoxical pain.[21] One had an M3G:M6G ratio of 8.17, having been on morphine for three weeks and on a dose of 180 mg per day. He had small-cell lung cancer and rapidly deteriorated and died three days after giving blood for the study. The second had an M3G:M6G ratio of 14.83, having been stabilized on 60 mg per day for a long period for celiac-plexus pain. Both of these patients had abnormal liver function tests. The other patient who had a high M3G:M6G (14.95) (Figure 5), had undetectable amounts of morphine and low concentrations of M3G (127 nmol per L) and M6G (8 nmol per L) on 30 mg per day of morphine, with complete pain relief. One further patient in this study subsequently appeared to develop paradoxical pain from recurrent squamous cell carcinoma of the cervix with induration of the left vaginal wall associated with neuropathic pain. At the time she gave blood for this study her pain was well controlled and the M3G:M6G was 5.49. The subsequent M3G:M6G was 9.41.

DISCUSSION

This study represents a snapshot of a limited number of pharmacokinetic parameters in a relatively typical group of hospital patients with cancer receiving morphine.

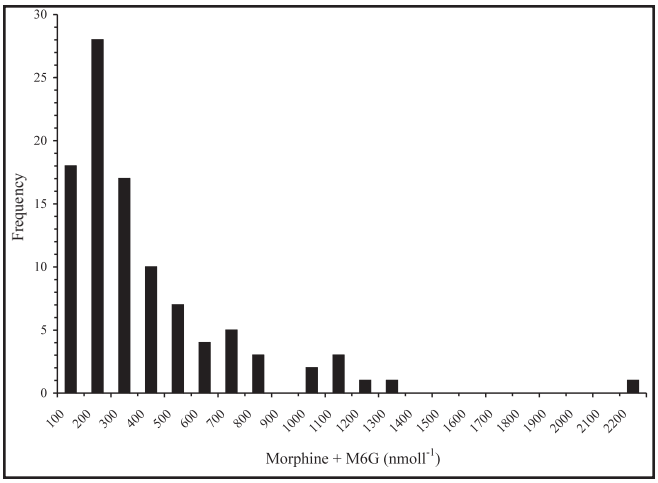

Figure 3. Distribution of plasma concentrations of morphine + M6G.

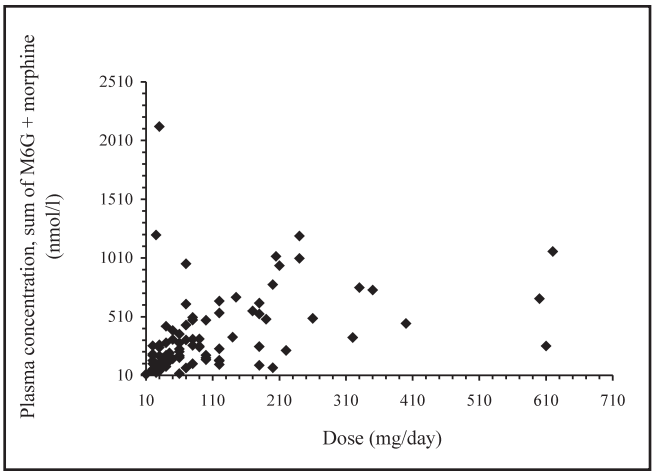

Figure 4. Relationship of dose to [M6G + morphine].

It seems likely that the conclusions from this study could be extrapolated to the wider group of patients on oral morphine. Although M6G is a potent analgesic,[11,15] little is known of the relative contributions of morphine and its metabolites to analgesia and toxicity, and it is obviously impossible to unravel those with a single assay of plasma concentrations. Furthermore, there is no assurance that patients were titrated to optimal or maximally tolerated doses of morphine, and there was no prospective coherent policy for the use of coanalgesics. There are significant limitations inherent in the study design that limit interpretation. Despite this and the inherent danger in performing multiple analyses on a large number of variables, important conclusions can be drawn from this study. M6G appears to contribute significantly to the analgesic potency of oral morphine. For the vast majority of patients, the M3G:M6G ratio is relatively narrow and does not predict for analgesia or toxicity. Even in the upper quartile of the distribution of M3G:M6G, patients were nearly three times as likely to have good as opposed to poor pain relief.

The literature also supports a relatively narrow range of morphine metabolite ratios. In two single-dosing studies of oral morphine in normal volunteers using sufficiently specific methodology to differentiate morphine from M6G, the ratio of M3G:M6G was 5.87:1[3] and 8.08:1.[30] In studies undertaken on patients with reasonably well controlled pain established on oral morphine the plasma M3G:morphine ratios ranges from 4.5:1 to 9.1:1 with a mean of 6.56 (± 1.84).[31-35] Morley et al. were the first to report elevated M3G:M6G ratios in a limited pharmacokinetic analysis of a series of patients with poorly opioid–responsive pain.[36] In 20 patients whose pain had been unsatisfactorily controlled by large doses of opioids, M3G:M6G plasma ratios appeared to be greater than the mean for the normal population, quoted as 5:1. In four of the patients with particularly difficult pain, they found plasma M3G:M6G ratios > 10, with the largest ratio being 35:1. Subsequently, there have been four other studies in patients with poorly controlled pain that have shown ratios similar to those reported in the current study and similar to the values seen in patients in other studies with well-controlled pain. Mean M3G:M6G ratios were 4.44,[37] 5.84,[38] 6.30,[39] and 6.74,[34] an overall mean of 5.83 (± 1.00). These studies also reported cerebrospinal fluid ratios, which ranged from 2.5 to 9.13.

The concepts of paradoxical pain or functional antagonism of morphine metabolites are supported by the differential induction of UDPGT isoenzymes, differences in the K_{max} of isoenzymes that catalyze M3G and M6G production, and the pediatric ratio data. Although UDPGT clearly exists as a number of isoenzymes, such small variation in the ratio of metabolites is very unlikely to owe to polymorphism of the enzyme. There is evidence for heterogeneity of UDPGT with the rat liver glucuronidating relatively more (-)-morphine and the converse being found in human liver[40] in line with the observation that M6G is a far more prevalent metabolite in humans[3,7] than in the rat.[40] Differential induction of UDPGT isoenzymes has been reported for detergents,[41] metal ions,[42] centrally acting drugs,[43] and clofibrate.[35] The differential induction of an isoenzyme may be a reasonable explanation, although there is as yet no direct evidence to support genetic polymorphism or differential induction of isoenzymes influencing the metabolism of morphine. Indeed, the current view is that UDPGT B7 glucuronidates at both positions and the isoforms UGT2B7Y and H do not account for the variability in the plasma or urine concentrations of these glucuronides in human populations.[44,45] One reason for selecting greater than two hours post-morphine administration as the cutoff for blood sampling was the observation that M3G and M6G have slightly different mean t_{max} after the administration of oral morphine to normal volunteers[3] of 1.4 (± 0.5) and 1.25 (± 0.4) hours, respectively, and that there is an increased M3G:M6G ratio during the first 30 minutes after IV morphine

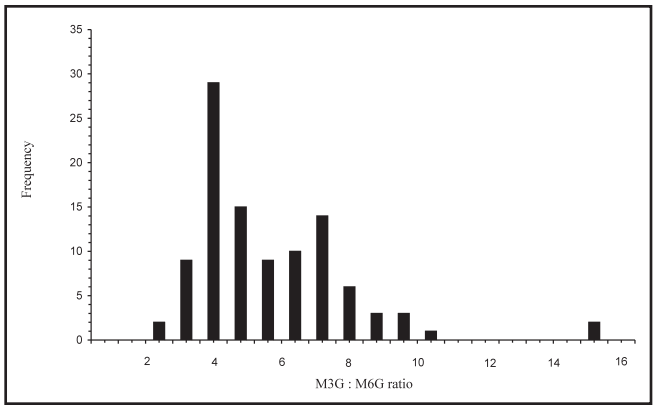

Figure 5. Frequency distribution of M3G:M6G ratio.

and one hour after oral morphine.[3] Therefore, M3G is not only produced in larger amounts, but also more quickly than M6G. This is more likely explained by the relative ease of glucuronidation at the 3 position on the phenanthrene ring, however, in line with in vitro work that reported the mean rate of production of M3G (V_{max}) as 0.94 (mol per min per mg) and that of M6G as 0.13 (mol per min per mg).[31] It is possible that this discrepancy of V_{max} explains Hartley et al.'s observation of altered ratios associated with the premature liver.[46] In this study, no alteration of the M3G:M6G ratio with dose was observed. This is not surprising, as the capacity of human liver glucuronidation of morphine reported in vitro is almost 10,000 times greater than the maximum plasma concentration of morphine in this study, a K_m of approximately 2 mmol per L.[30]

In this study, pain was generally well controlled, with effective pain relief in more than 80 percent of patients. Patients with pain that is difficult to control, most typically neuropathic or incident (i.e., precipitated by locomotor activity) pain, are commonly treated with an increasing number of drugs, and the finding of an association of NSAIDs and antiepileptic medications with excess toxicity is perhaps not surprising. The association of higher concentrations of plasma morphine with tricyclic antidepressants has been described, and may owe to a direct effect on liver metabolism. Indeed, this may be a pharmacokinetic explanation for some of the improvement in morphine–poorly responsive pain, for which they are often used.[43] A more likely explanation, however, is that patients with worse pain had higher morphine concentrations because of higher doses of oral morphine. Although the numbers are small, there appeared to be no data to support an alteration in M3G:morphine or M3G:M6G ratios in patients on tricyclic antidepressants.

It is apparent that the glucuronides can, when present in very large amounts, cause considerable toxicity.[8] A number of population studies have reported a correlation between renal dysfunction and steady-state M6G or morphine concentrations,[33,34,47,48] but none has demonstrated a correlation between specific side effects and higher metabolite concentrations. Tiseo et al. reported a moderate but significant correlation between the M6G:morphine ratio and urea ($r = 0.4$, $p < 0.001$) and creatinine ($r = 0.45$, $p < 0.001$) concentrations, but not with other clinical variables in 109 cancer patients on oral and parentral morphine.[47] Obtundation was more commonly associated with liver dysfunction than with renal impairment, and while seven of nine episodes of respiratory depression or obtundation were associated with M6G concentrations of >4 mmol per L, 13 further patients had similarly high concentrations of M6G but normal biochemistry and minimal toxicity. In a smaller study in which plasma M3G and M6G concentrations were significantly ($p < 0.001$) higher in patients with elevated serum creatinine concentrations, this was concluded to be an aggravating factor in the nausea and vomiting and cognitive function profile of palliative and terminal care patients with significant renal function impairment.[47]

A number of investigators have attempted to correlate plasma concentrations of morphine with measures of analgesia in similar point-prevalence studies. Tiseo et al. found that metabolic dysfunction was a better predictor of myoclonus and cognitive impairment than an increased M6G:morphine ratio.[47] Faura et al. reported that M6G + morphine concentrations in their "optimally controlled" group were more than twice those in the "moderate control" group [751 (± 194) vs. 277 (± 42) nmol per L) and suggested a threshold of 400 nmol per L for optimal analgesia.[2] In a smaller study of 40 patients starting slow-release morphine, the mean trough serum morphine concentration associated with pain relief was 66 nmol per L.[49] In our study, although a similar relationship was found, it was not possible to define a specific threshold.

The extraordinarily large dose range for morphine has been interpreted as evidence for the development of tolerance.[33] This study reports a significant correlation between dose and time on morphine ($p = 0.04$). It has generally been concluded that the escalation in dose relates to worsening pain to a greater extent than to the development of tolerance, and there is little evidence for addiction in cancer patients on morphine. There was no correlation between M3G:M6G ratio and duration of treatment ($p = 0.65$) in contrast with the observation that M3G appeared to correlate with the development of tolerance in different infusion regimens in rats.[22] In fact, Smith and Smith's study was constructed such that an effect of different exposures to morphine could not be excluded and appears to be a more likely explanation for the observation.

Morphine remains one of the central treatments for cancer-related pain. An improvement in our understanding of the metabolism of morphine during the last 25 years has revealed the importance of M6G as an active metabolite. There is still very little evidence to implicate

M3G in tolerance or an adverse therapeutic profile in even a very small minority of patients. Our experience in normal volunteers very much suggests that M3G is devoid of significant activity.[50] Although further pharmacokinetic-pharmacodynamic modeling may help our understanding of the analgesic effects of morphine and M6G, the challenge now is to develop M6G analogs to benefit patients rather than simply rely on endogenous M6G production from morphine.

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