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PHARMACODYNAMICS

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Start of oral morphine to cancer patients: effective serum morphine concentrations and contribution from morphine-6-glucuronide to the analgesia produced by morphine

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Abstract *Objective*: To investigate the serum concentrations of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) and the relationships between serum concentrations and clinical effects associated with start of morphine treatment in cancer patients.
Methods: Forty patients with malignant disease and intolerable pain on weak opioids (codeine/dextropropoxyphen) were included. After a wash-out period, titration with immediate-release (IR) morphine was started. When a stable dose was achieved, the morphine treatment was changed to slow-release (SR) morphine in equivalent daily dosages. Clinical data and serum concentrations of morphine, M3G and M6G were obtained at the end of the IR and SR morphine treatment periods.
Results: The mean trough serum morphine concentration associated with pain relief was 66 nmol/l. The corresponding mean concentrations of M6G and M3G were 257 nmol/l and 1943 nmol/l, respectively. Morphine serum trough concentrations showed a 33-fold variation. Seventy percent of the variation was predicted in a model including age, daily morphine dose and M6G/morphine ratio as independent variables. No associations were observed between side effects and serum concentrations of morphine and its metabolites.
Conclusion: In this study, a mean serum trough morphine concentration of 66 nmol/l was associated with satisfactory pain relief when disease progression required an increase in intensity of pain therapy from step II to step III in the World Health Organization pain ladder. An increased ratio of M6G to morphine serum concentrations predicted lower effective serum morphine concentrations at the time of satisfactory pain relief. This observation supports that M6G contributes to the pain control produced by oral morphine in patients with pain caused by malignant disease.

Key words Pain · Cancer · Morphine metabolites

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Introduction

Morphine is degraded in the liver to several metabolites, of which morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) are considered biologically active [1]. Studies have demonstrated M6G affinity to μ-opioid receptors, M6G to produce antinociception in animal experimental models and a contribution from M6G to analgesia produced by morphine in cancer pain treatment [2, 3, 4, 5]. In contrast, other studies did not observe analgesic effects of M6G in postoperative pain or a relationship between M6G concentrations and morphine-related side effects [6, 7]. Studies of M3G effects are also conflicting, since some studies report anti-analgesic or exitatoric effects of M3G while other studies do not reveal such effects [8, 9, 10].

Previous studies during chronic morphine therapy in cancer pain patients report large inter-individual variability of morphine, M3G and M6G serum concentrations (ranges: morphine 2–3497 nmol/l; M3G 41–51060 nmol/l; M6G 0–10976 nmol/l) [11, 12, 13, 14, 15, 16]. The variability observed in these studies is partly caused by the inclusion of patients from all stages of cancer disease, hence using morphine in variable dosages (10–2540 mg/24 h) and for variable durations (3–1095 days).

Studies measuring morphine and metabolites serum concentrations at a defined stage of pain progression are needed to assess the pharmacokinetic variability between cancer patients, which is not influenced by

comparing patients from various stages of cancer disease. Also, the effective serum concentrations of morphine and metabolites associated with satisfactory analgesia at the time of morphine introduction according to the World Health Organization (WHO) guidelines [17, 18] have, to our knowledge, not been previously reported. Thus, the primary aim of this study was to investigate the serum concentrations of morphine and its metabolites necessary to achieve analgesia after initiating step III of the WHO pain ladder. The secondary aim was to investigate the explanatory variables to the inter-individual variability of serum morphine concentrations.

Methods and patients

Patients

Forty patients with malignant disease and moderate or severe pain despite receiving weak opioids were prospectively included in the study. The exclusion criteria precluding participation in the study were decreased gastrointestinal uptake of oral medications or reduced cognitive function (e.g. dementia, psychiatric disease).

At the time of entering into the study the patients used weak opioids corresponding to step II of the WHO pain ladder. The weak opioids were either codeine–acetaminophen (codeine 60 mg × 4 plus acetaminophen 800 mg × 4) ($n = 34$) or dextropropoxyphen–acetaminophen (dextropropoxyphen 140 mg × 4 plus acetaminophen 800 mg × 4) ($n = 6$) combinations. Five patients also used additional nonsteroidal anti-inflammatory drugs (NSAIDs). Weak opioids in combination with acetaminophen were stopped at the time of inclusion, while NSAIDs were continued in stable dosages. During the study period, 14 patients received fractionated radiotherapy (bone metastasis 8, lymph nodes 5, pulmonary metastasis 1). Sixteen patients used chemotherapy, hormone treatment (6 patients) or cytotoxic therapy (10 patients), at study entry. All patients received a bowel regimen of a stimulant laxative, bisacodyl, plus a stool softener, lactulose. No prophylactic anti-emetic drugs were administered.

Study design

The study period was divided into three parts, as illustrated in the trial profile in Fig. 1.

Period 1: wash-out period

The wash-out period lasted for 2 days. During this period, the patients did not obtain any regularly scheduled opioids but were allowed to request rescue analgesics.

Rescue medication for pain both during the wash-out and the morphine treatment periods was oral ketobemidone, a μ-opioid receptor agonist with a potency comparable to that of morphine. The ketobemidone rescue dose was conventionally set to 5 mg. In cases in which 5 mg ketobemidone had inferior analgesic effect, an increased dose of 10 mg was applied. Ketobemidone was chosen as rescue medication in order to avoid the confounding effects from rescue analgesics on the morphine and morphine metabolite analyses. To avoid increased complexity of the protocol, the ketobemidone dose was not related to the total daily morphine dose. No limits with respect to number of daily doses or lockout interval between rescue medications were defined.

Period 2: titration with immediate-release morphine

After completion of the wash-out period, the patients started with oral immediate-release (IR) morphine (10 mg every 4 h). The oral morphine doses were increased daily according to a fixed schedule

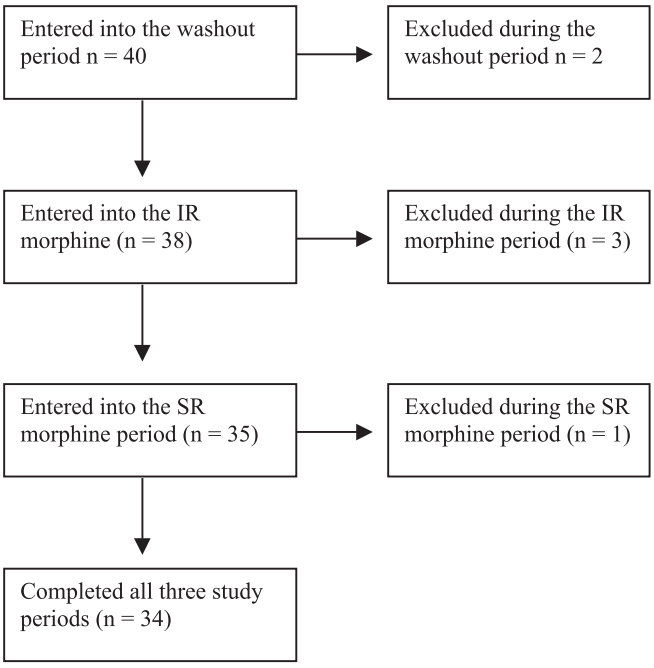

Fig. 1 Patient flow and patient exclusions through the wash-out, immediate-release (*IR*) morphine and slow-release (*SR*) morphine periods

(10 mg × 6, 15 mg × 6, 20 mg × 6, 30 mg × 6, 45 mg × 6, 60 mg × 6) until the patient reported satisfactory pain relief. Satisfactory pain relief was defined by no, near unnoticeable or little pain on the verbal rate scale (VRS) score and not more than two daily requests for rescue analgesics. If necessary, due to sedation (the patient choosing a delay of upward titration of morphine dose due to tiredness), a scheduled dose increase was postponed for 1 day. The study period two lasted for a minimum of 4 days and a maximum of 7 days. The elimination half-life values ($t_{1/2}$) of morphine, M6G and M3G are reported to be 2.7, 2.7 h and 3.5 h, respectively [1]. Consequently, to ensure steady-state conditions, all patients had at least used morphine in stable doses for 2 days before study period 2 was concluded.

Period 3: slow release morphine

After the completion of study period 2, IR morphine was replaced with slow-release (SR) morphine (Dolcontin), administered three times daily in the same total daily doses as the final titrated IR morphine dose. SR morphine was administered in unaltered dose for 3 days.

Pain scores

During the study, pain was assessed once daily using a seven-point VRS score (1 – no pain; 2 – near unnoticeable pain; 3 – little pain; 4 – moderate pain; 5 – severe pain; 6 – very severe pain; 7 – unbearable pain) and a visual analogue scale (VAS) score (10 cm, anchored with 0 – no pain and 100 – unbearable pain). The patients were asked to rate their average pain for the last 24 h. The daily use of rescue analgesics was also recorded.

Side-effect scores

Nausea, sedation, constipation, loss of sleep and tremor were assessed by means of a four-point VRS score (1 – not at all; 2 – some;

3 – severe; 4 – very severe). The patients were asked to rate their average symptoms for the last 24 h.

Plasma sampling and analyses

Blood samples were collected just prior to, 45 min after and 90 min after administration of IR morphine, and just prior to, 2 h after and 4 h after SR morphine administration. The times for collecting samples were decided in order to obtain trough serum concentrations and approximately maximum serum concentrations of morphine (IR morphine 45 min, SR morphine 2 h) and metabolites (IR morphine 90 min, SR morphine 4 h) using peak plasma concentration (C_{max}) values reported in previous studies [16, 19, 20, 21]. The samples were collected on the last day in the IR and SR morphine treatment periods.

Serum samples were stored at −20 °C until the analyses were performed. The concentrations of morphine (morphine base), M3G and M6G were determined by reverse-phase high-performance liquid chromatography (HPLC) with ultraviolet and electrochemical detection [22, 23]. The lower limits of quantification were as follows: morphine 10 nmol/l, M3G 100 nmol/l and M6G 10 nmol/l. The coefficients of variation were for morphine 8.9, for M6G 5.4 and for M3G 6.9.

Ethics

The Regional Committee for Research Ethics, University of Trondheim approved the study, and all patients gave their oral and written informed consent before inclusion in the study.

Statistics

Data are presented as means, standard deviations and ranges if not otherwise specified. Pain and symptom VRS and pain VAS scores are compared applying the Wilcoxin rank sum test. Consumption of rescue ketobemidone and serum concentration values is compared using the Student's *t*-test for paired data.

Associations between serum concentrations of morphine and its metabolites with each other and with effect variables are performed using Spearman's rank-order correlation test. Due to multiple comparisons, values of P lower than 0.01 were considered significant. Factors predicting variability of morphine serum concentrations were analysed using a backward stepwise regression analysis with a criterion of probability of F, 0.10, for removal.

The statistical software SPPS for Windows 95 v8.0 was used throughout the analysis.

Results

Patient characteristics

The characteristics of the patients are presented in Table 1. During the study period, six patients were excluded from the study due to acute relapse of panic disorder (1), acute surgery (1), acute compression of the spinal cord (1), spontaneous remission of pain (1) and death (2) (Fig. 1). No patient exclusions were caused by morphine side effects.

The mean daily oral titrated morphine dosage was 97 ± 43 (60–180) mg. The patients pain scores and use of rescue pain medication decreased after start of morphine, while there were no differences in pain intensity between the IR and SR morphine period (Table 2). Constipation increased significantly after the start of morphine, while other symptom scores did not change (Table 2).

Table 1 Patient characteristics. Data are presented as number of patients or as mean ± standard deviation (range)

Male/Female	21/19
Mean age (range) (years)	63 ± 12 (34–78)
Cancer diagnosis	
Breast	9
Prostate	7
Gastric	3
Colon	8
Myeloma	3
Bladder	2
Pancreatic	2
Others	6
Metastasis	
Bone	18
Liver	11
Others	5
Karnofsky score (range)	68 ± 11 (40–90)
Months (range) from diagnosis	24 ± 32 (0–109)
Months (range) from start of uncontrolled pain	4.3 ± 4.3 (0.5–18)

Serum morphine concentrations after IR morphine titration

Table 3 presents the serum concentrations of morphine after titration with IR morphine. Just prior to intake, the mean serum morphine concentration (trough concentration) was 66 ± 47 nmol/l. The variation between individuals was considerable, with the lowest morphine serum concentration being 7 nmol/l and the highest 212 nmol/l. The trough morphine serum concentrations showed a significant positive correlation with daily morphine dosage ($r = 0.67$, $P < 0.001$) (Fig. 2). When serum morphine concentrations were adjusted with respect to daily morphine dose, the inter-individual variability was still considerable (range 11–177 nmol/l/100 mg daily morphine).

The inter-individual variation of IR morphine trough serum concentrations giving satisfactory pain relief (dependent variable) was analysed in a multiple linear regression model applying daily morphine dose, age, gender, M6G/morphine ratio and M3G/morphine ratio as independent variables. This analysis resulted in a model, including the variables daily morphine dose, age and M6G/morphine ratio, which explained 70% ($r^2 = 0.704$) of the observed variability in IR morphine trough serum concentrations. Both daily morphine dose (Fig. 2) and age showed a positive relationship with morphine serum concentrations, while the M6G/morphine ratio showed a negative relationship with morphine serum concentrations (Fig. 3) (standardised β coefficients 0.50, 0.37 and −0.60, respectively).

Serum concentrations of metabolites after IR morphine titration

Table 3 presents the serum concentrations of M3G and M6G after titration with IR morphine. The mean serum

Table 2 Pain and symptoms scores. Pain is expressed using visual analogue scale (VAS) scores (0 – no pain; 100 – unbearable pain). Other symptoms in verbal rate scale (VRS) scores (1 – not at all; 2 – some; 3 – severe; 4 – very severe). All data are presented as mean ± standard deviation (range)

	Wash-out period	Immediate-release morphine period	Slow-release morphine period
Pain (VAS)	32 ± 19 (1–91)	16 ± 14 (0–50)	18 ± 13 (0–51)
Ketobemidone rescue (mg/24 h)	29 ± 16 (5–70)	4 ± 8 (0–30)	6 ± 9 (0–35)
Nausea (VRS)	1.4 ± 0.7 (1–4)	1.4 ± 0.7 (1–3)	1.6 ± 0.7 (1–3)
Sedation (VRS)	1.9 ± 0.7 (1–3)	2.2 ± 0.9 (1–4)	2.1 ± 0.8 (1–4)
Constipation (VRS)	1.4 ± 0.8 (1–4)	2.0 ± 1.1 (1–4)	1.8 ± 0.9 (1–4)
Loss of sleep (VRS)	1.3 ± 0.6 (1–3)	1.5 ± 0.5 (1–3)	1.5 ± 0.6 (1–3)
Tremor (VRS)	1.2 ± 0.4 (1–2)	1.2 ± 0.5 (1–3)	1.3 ± 0.6 (1–3)

trough concentrations after IR morphine titration of morphine metabolites were 1943 ± 1070 (551–5223) nmol/l M3G and 257 ± 149 (63–818) nmol/l M6G. Both M3G and M6G trough serum concentrations showed a moderate correlation with daily morphine dose (M3G $r = 0.47$, $P < 0.01$; M6G $r = 0.55$, $P < 0.001$) (Fig. 2). The mean ratios between M6G/morphine, M3G/morphine and M3G/M6G serum concentrations were 5.4 ± 3.9 (1.2–17.6), 39.3 ± 29.4 (9.8–140.3) and 7.8 ± 2.3 (2.5–13.7), respectively. The observed ratios 45 min and 90 min after morphine intake were unchanged from the trough ratios (Table 4).

Serum concentrations of morphine and metabolites after SR morphine

The serum concentrations of morphine and its metabolites 3 days after changing from IR to SR morphine are presented in Table 3. Mean serum trough concentrations after SR morphine were 64 ± 55 (9–267) nmol/l morphine, 1681 ± 1415 (619–6922) nmol/l M3G and 219 ± 203 (67–1092) nmol/l M6G. Peak serum concentrations after SR morphine were 99 ± 61 (18–283) nmol/l morphine, 2269 ± 1570 (945–8451) nmol/l M3G and 301 ± 218 (107–1162) nmol/l M6G. There were no significant differences between the IR and SR morphine observations (Table 3). The ratios between morphine and its metabolites after SR morphine are presented in Table 4. These results were similar to the results after IR morphine. In parallel with the results after IR morphine, the serum concentrations of morphine, M3G and M6G showed a significant correlation with total daily SR morphine dosage (data not shown).

The inter-individual variation of SR morphine serum trough concentration giving satisfactory pain relief (dependent variable) was also analysed in a multiple linear regression model including daily morphine dose, age, gender, M6G/morphine ratio and M3G/morphine ratio as independent variables. This analysis after SR morphine replicated the result after IR morphine with a model including daily morphine dose, age and M6G/morphine ratio explaining 47% ($r^2 = 0.467$) of the observed variability in morphine serum concentrations at the time of satisfactory pain relief. Also, after SR morphine, both daily morphine dose and age showed a positive relationship with morphine serum concentration, while the M6G/morphine ratio showed an inverse relationship with morphine serum concentrations (standardised β coefficients 0.46, 0.38 and −0.46, respectively).

Relationships between serum concentrations and ratios of morphine, M3G and M6G to clinical effects

Higher pain intensity significantly correlated with higher IR serum trough concentrations of morphine ($r = 0.47$). No significant association between pain intensity and M3G or M6G IR serum trough concentrations were observed. Pain intensity also showed no significant relationships to the ratios between morphine and metabolites.

Table 3 Serum concentrations of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). All data are presented as mean ± standard deviation (range)

	Immediate-release morphine		Slow-release morphine	
	Time (min)	Concentration	Time (h)	Concentration
Morphine (nmol/l)	0	66 ± 48 (7–213)	0	64 ± 55 (9–267)
	45	76 ± 46 (6–220)	2	99 ± 61 (18–283)
	90	75 ± 41 (22–196)	4	88 ± 56 (27–272)
M3G (nmol/l)	0	1943 ± 1070 (551–5223)	0	1681 ± 1414 (619–6921)
	45	2109 ± 1672 (579–9827)	2	2217 ± 1371 (685–6749)
	90	2043 ± 1375 (806–7890)	4	2269 ± 1570 (945–8451)
M6G (nmol/l)	0	257 ± 149 (63–818)	0	219 ± 203 (67–1091)
	45	297 ± 232 (77–1317)	2	287 ± 190 (82–1106)
	90	267 ± 186 (93–1041)	4	301 ± 218 (107–1161)

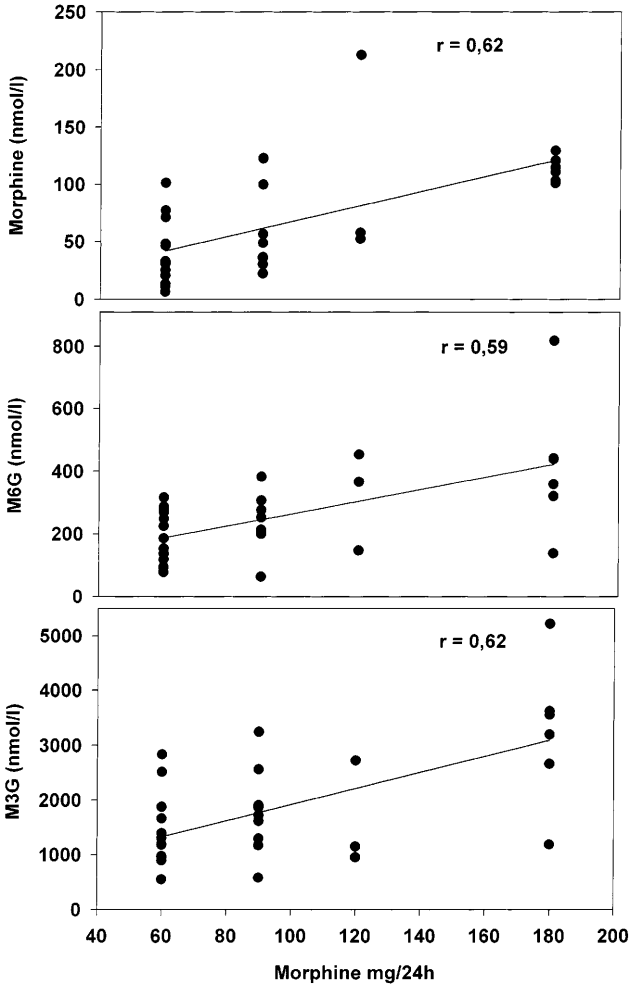

Fig. 2 Relationships between daily morphine dose and trough concentrations of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) after immediate-release morphine. Simple linear regression curves and *r* values are included in the figures

None of the side effects – nausea, sedation, loss of sleep, tremor or constipation – showed any significant association with the IR serum trough concentrations or ratios of morphine, M3G and M6G. Also, the corresponding observations 45 min and 90 min after IR morphine administration and at all time points after SR morphine were not significantly correlated to the intensity of side effects.

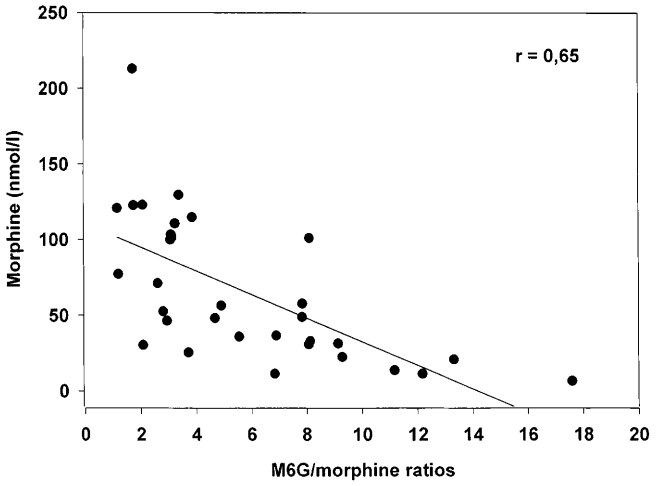

Fig. 3 Relationships between serum trough morphine concentrations and morphine-6-glucuronide (M6G)/morphine ratios at the time of satisfactory pain relief after titration with immediate-release morphine. The figure illustrates that patients with a high morphine serum concentration and low degree of metabolism to M6G had the same pain relief as patients with low morphine serum concentrations and a higher degree of metabolism to M6G. Simple linear regression curve and *r* value are included in the figure

Discussion

This study defines serum concentrations of morphine and its metabolites associated with pain control after start of IR morphine according to the WHO guidelines. The observed mean serum concentration of 66 nmol/l just prior to morphine intake (trough concentration) can be considered to approximately define the lowest effective serum concentration, giving a patient pain relief at this defined stage of pain progression. The morphine serum concentration observed in our study was about one-quarter of that observed in studies by McQuay et al. and by Faura et al. (275 nmol/l and 244 nmol/l, respectively), about half of that in a study by Ashby et al. (140 nmol/l) and equal to that in a study by Wollf et al.

Table 4 Serum ratios of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). All data are presented as mean ± standard deviation (range)

	Immediate-release morphine		Slow-release morphine	
	Time (min)	Ratio	Time (h)	Ratio
M6G/Morphine	0	5.4 ± 4.0 (1.2–17.6)	0	5.2 ± 6.7 (0.5–32.1)
	45	4.3 ± 3.8 (0.9–18.1)	2	3.4 ± 4.5 (1.0–26.9)
	90	4.4 ± 3.3 (0.8–15.2)	4	4.0 ± 2.8 (1.2–15.8)
M3G/Morphine	0	39.3 ± 29.3 (9.9–140.3)	0	36.8 ± 52.0 (4.5–267.7)
	45	31.0 ± 26.2 (9.3–135.1)	2	25.5 ± 38.7 (7.2–231.8)
	90	32.9 ± 22.3 (8.8–115.3)	4	30.2 ± 21.6 (8.9–131.6)
M3G/M6G	0	7.8 ± 2.3 (2.5–13.7)	0	8.2 ± 2.1 (3.6–14.2)
	45	7.8 ± 1.9 (2.4–11.1)	2	7.7 ± 1.5 (4.1–10.6)
	90	7.8 ± 2.0 (2.8–12.3)	4	7.8 ± 1.3 (5.1–10.7)

(67 nmol/l) [11, 12, 14, 15]. The most obvious explanation for the differences in morphine serum concentrations is that these studies included patients receiving long-term (range 3–1095 days) and high-dose (range 10–2540 mg/24 h) morphine treatment. However, duration and doses do not account for all differences, since dose-adjusted morphine serum concentrations in the studies by McQuay et al. and Faura et al. were twofold that of our results [11, 12].

The divergence between studies on morphine serum concentrations in cancer patients is most probably caused by heterogeneous patient populations. This combined with few patients in each study may result in selection bias. We believe that a more defined patient population is needed to obtain more precise estimates of morphine pharmacokinetics. Examples of criterion for defining such subpopulations are cancer diagnoses, age groups or specific stages in the patients' pain progression.

The observations in this study enable comparisons of the pain intensity leading to the start of strong opioids in cancer patients with other pain conditions. In a study of pain after major abdominal surgery, the calculated minimum effective concentration of morphine was 54 nmol/l [24]. Trough serum concentration (C_{min}) during oral morphine should not be regarded as equal to the concept of minimum effective serum concentration derived from studies applying intravenous patient-controlled analgesia. Still, it is of interest to observe that the C_{min} morphine concentration of 66 nmol/l observed in cancer patients just after the start of morphine treatment approximately equals the minimum effective concentration of morphine after major abdominal surgery. This illustrates that the pain intensity in cancer patients at this stage of disease is comparable to the pain intensity after abdominal surgery.

The individual morphine trough serum concentrations in our patient population varied from 7 nmol/l to 212 nmol/l and showed a standard deviation about two-thirds of the mean value. This 33-fold inter-individual variation was less than observed by Faura et al., Wollf et al. (standard deviations twofold of the mean) and Ashby et al. (standard deviation equal to the mean) [12, 14, 15]. The study by McQuay et al. did not specify a calculated measure of the spread of data but the observed range of 2–3497 suggests a considerable variation [11]. The lower inter-individual variation observed in our study is due to the fact that all patients experienced pain indicating an upwards increase in pain therapy from step II to III on the WHO pain ladder, a well-defined target of pain relief, exact defined times for obtaining blood samples, the use of standardised morphine formula and a well-defined duration of morphine treatment (4–7 days).

In our study, three variables, daily morphine dose, age and M6G/morphine ratio predicted 70% of the inter-individual variation of morphine trough serum concentration. The relationship between daily morphine dose and morphine serum concentrations confirms previous studies [11, 14, 15, 16, 25]. However, as illustrated in Fig. 2 for the individual patient, it is not feasible to predict serum concentrations of morphine from morphine intake.

A high concentration of M6G relative to morphine predicted lower serum concentrations of morphine at the time of satisfactory pain relief. This observation supports the putative role for M6G in morphine-induced analgesia. If M6G has a superior analgesic effect to morphine, it would be expected that patients who metabolise a larger fraction of morphine to M6G will need lower serum morphine concentrations in order to achieve pain relief. Our observation of a contribution from M6G in morphine analgesia is supported by a study by Faura et al. [12]. They observed that the level of morphine serum concentrations did not differentiate between patients with optimal versus moderate pain control, while a sum of morphine and M6G serum concentrations (405 nmol/l) could delimit patients with optimal pain control from those achieving moderate pain control. Also in support of a contribution from M6G to the analgesia produced by morphine is the positive relationship between pain relief and M6G/morphine ratio observed in patients receiving intravenous morphine for chronic pain (9 of 11 patients with cancer pain) [5].

The large inter-individual variability of ratios between morphine and metabolites serum concentrations in previous studies was also observed in our study [26]. This variability observed in patients using oral morphine only for a short period (4–7 days) and in low doses (60–180 mg/day) argues against the variability of ratios being caused by activation of metabolic systems during long-term morphine use or by a ceiling effect on the morphine degradation. The results in our study also confirmed previous observations, summarised in the systematic review by Collins et al., of serum concentrations and ratios of morphine and metabolites being equal during equivalent dosages of IR and SR morphine [20, 27, 28].

With the exception of a weak positive association between pain intensity and morphine serum concentrations, our study revealed no associations between clinical symptoms and pharmacokinetic observations. A possible explanation to the higher morphine serum concentrations in patients with higher pain intensity may be that some patients do not accept the optimal dose escalation. The patients may decide against dose escalation due to side effects or due to a prejudice against the use of morphine.

In one previous study, plasma M3G and M6G concentrations corrected for morphine dose were higher in patients who suffered nausea, vomiting or confusion, while the actual morphine, M3G and M6G concentrations and the ratios between these substances were the same [14]. These patients also had impaired renal function. Consequently, it cannot be excluded that impaired renal function was the common cause for both the reported symptoms and the pharmacokinetic observations [14]. Other studies on patients with malignant disease

including ours do not establish a consistent relationship between symptoms believed to represent morphine side effects and pharmacokinetics of morphine [7, 12, 29]. A limitation in both ours and other studies is relatively small sample sizes, which imply that the lack of a positive association between clinical symptoms and pharmacokinetics of morphine metabolites can be due to limited statistical power. A study including a larger number of patients is needed to draw a firm conclusion regarding this topic.

In conclusion, in this study of a homogeneous cancer-pain patient population, we observed lower inter-individual variations of morphine serum concentrations than previously reported. The mean serum trough morphine concentration sufficient to relieve pain in patients entered into step III of the WHO ladder for cancer pain control was 66 nmol/l. An increased ratio of M6G vs morphine serum concentrations predicted lower effective serum morphine concentrations. This observation supports the hypothesis that M6G contributes to the analgesia produced by oral morphine in patients with pain caused by malignant disease.

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