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PHARMACOKINETICS AND DISPOSITION

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Variability of morphine disposition during long-term subcutaneous infusion in terminally ill cancer patients

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Abstract *Objective*: To study the plasma concentrations of morphine and its glucuronides to assess the intra- and interindividual variability of the disposition of morphine administered by subcutaneous infusion in cancer patients.
Methods: Blood samples were taken repeatedly in eight patients with severe cancer pain who were being treated with morphine (60–3000 mg per day) via chronic (8–160 days) subcutaneous infusion. Venous blood samples were collected at least weekly and, when possible, on 3 consecutive days after dose adaptation or any other major change in the patients' treatment. Concentrations of morphine and its glucuronides in plasma were measured after solid-phase extraction using a validated high-performance liquid chromatography assay. The stability of the morphine solutions was determined by repeated measurement of the concentrations of morphine and its degradation products in the solutions.
Results: The morphine concentration in the infusion solutions remained unchanged during storage and infusion. The plasma concentrations of morphine and its glucuronides were within the ranges reported in the literature. There was, as expected, a large interindividual variability: from patient to patient, the mean of the normalised plasma concentrations ranged from 0.3 $ng \cdot ml^{-1} \cdot mg^{-1}$ to 0.8 $ng \cdot ml^{-1} \cdot mg^{-1}$ for morphine, from 1.0 $ng \cdot ml^{-1} \cdot mg^{-1}$ to 3.1 $ng \cdot ml^{-1} \cdot mg^{-1}$ for morphine-6-glucuronide and from 6.8 $ng \cdot ml^{-1} \cdot mg^{-1}$ to 24.3 $ng \cdot ml^{-1} \cdot mg^{-1}$ for morphine-3-glucuronide. Intra-individual variability was also important. The residual standard deviation of the mean normalised plasma concentrations calculated for each patient ranged from 26% to 56% for morphine, from 20% to 51% for morphine-6-glucuronide and from 20% to 49% for morphine-3-glucuronide. The normalised plasma concentrations of morphine and its glucuronides did not increase with dose or time, and no explanation for the pronounced pharmacokinetic intraindividual variability was found.
Conclusion: During subcutaneous infusion of morphine, there is a large intra- and interindividual variability of the morphine disposition which could be of clinical relevance.

Key words Morphine disposition, Cancer patients, Subcartaneous infusion

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Introduction

When the oral route is no longer satisfactory, morphine is often given by subcutaneous infusion for pain control in terminally ill patients, but the intra- and inter-individual variability in dose requirements, need for dose adaptation, efficacy and adverse effects are also important [1]. The factors responsible for this variability are often not understood. In addition to changes in the underlying processes, lack of stability of the solutions and variability in absorption or metabolism could be involved. There are few data available regarding plasma concentrations during subcutaneous infusion of morphine. We therefore measured the plasma concentrations of morphine and its 3- and 6-glucuronides (M-3-G, M-6-G) in terminally ill cancer patients during long-term subcutaneous infusion of morphine to assess the intra- and the interindividual variability of its disposition. To exclude stability problems, the morphine-infusion solutions were repeatedly assayed.

Materials and methods

Subjects

The study protocol was approved by the ethics committee of the Gent University Medical School. Ten patients receiving chronic, subcutaneous infusion of morphine for severe cancer pain were included in the study. All patients started treatment at the hospital, but did not always stay in the hospital during the entire study period. The subjects gave oral informed consent. Two patients died within a few days of inclusion in the study, and our analysis is therefore restricted to the eight patients whose characteristics are described in Table 1. In patient GL, the subcutaneous infusion was interrupted from day 55 to day 70, because of the presence of hard discs at the infusion sites. All patients were also treated with several other drugs, mainly corticosteroids, hypnotics, laxatives and antiemetics, the dose of which was adapted depending on the symptoms.

Procedure

At the moment of inclusion in the study and at regular time intervals during the study, haematocrit, creatinine, albumin, total protein, alpha-1-acid glycoprotein, gamma glutamyl transferase, aspartate aminotransferase and alanine aminotransferase were determined in plasma using standard methods. Morphine infusions were administered using a Graseby syringe driver (Type MS). A 17- or 21-gauge butterfly needle or a Vialon catheter was inserted subcutaneously into the anterior chest or abdomen wall and was repositioned if irritation at the infusion site occurred. The dose of morphine was adapted by the attending physician depending on the degree of pain and adverse effects. The infusion rate ranged from 0.3 $ml \cdot h^{-1}$ to 4 $ml \cdot h^{-1}$. For dose adaptation, either the volume infused per unit time or the concentration of morphine hydrochloride in the syringe (range 3–56 $mg \cdot ml^{-1}$) was changed. The morphine hydrochloride (Belgopia, Louvain-La-Neuve, Belgium) solutions were prepared at the hospital pharmacy in polypropylene syringes (Becton Dickinson Benelux, Aalst, Belgium). Other drugs (maximum of two) were frequently added to the syringe: midazolam hydrochloride, ketamine hydrochloride, methylprednisolone sodium hemisuccinate, clonidine hydrochloride or hyalase. To exclude loss of substance due to incompatibilities or instability during storage of the syringe and during the infusion, 1-ml samples were taken from each syringe immediately after preparation, at the beginning and at the end of the infusion period, and whenever blood sampling was carried out. Some of these samples could not be obtained due to time limitations within the hospital or because of patients staying at home. Blood samples were taken either via a catheter in the superior caval vein or from a peripheral vein and were collected into ammonium–heparin polypropylene tubes (Sarstedt, Nümbrecht, Germany). Blood samples were obtained at least weekly; when possible, sampling was also carried out on 3 consecutive days after dose adaptation or any other major change in the patients' treatment. Samples were never taken within the first 24 h after dose adaptation. The blood samples were immediately centrifuged at 3000 g for 10 min and plasma was stored in borosilicate glass tubes at −20 °C until analysis, which was always performed within 70 days of sampling. Plasma samples containing morphine and its glucuronides can be stored at −20 °C without any loss for at least 6 months [2, 3].

Analytical procedures

The concentrations of morphine and its possible degradation products (pseudomorphine, morphine-*N*-oxide and apomorphine) in the infusion solutions were measured by a validated ion-pair reversed-phase high-performance liquid chromatographic (HPLC) method with UV detection at 254 nm [4]. Separation was obtained on an Ultrasphere RP-C_{18} column (5 μm, 250 × 4.6 mm, Beckman Instruments, Fullerton, Calif., USA), using a mobile phase consisting of 37.5% (v/v) acetonitrile in water containing 5 $mmol \cdot l^{-1}$ sodium dodecyl sulphate and 0.08 $mol \cdot l^{-1}$ ammonium acetate brought to pH 4.1 with anhydrous acetic acid at a flow rate of 1 $ml \cdot min^{-1}$. The within- and between-day coefficients of variation were below 2% for morphine (500–1000 $\mu g \cdot ml^{-1}$), below 10% for pseudomorphine (0.2–20 $\mu g \cdot ml^{-1}$) and morphine-*N*-oxide (0.5–10 $\mu g \cdot ml^{-1}$), and below 20% for apomorphine (0.5–10 $\mu g \cdot ml^{-1}$). Injection of the drugs added to the morphine solutions, under the same chromatographic conditions, was carried out in order to exclude interference with the determination of morphine and its degradation products.

The concentrations of morphine and its glucuronides in plasma (100 μl–1 ml) were determined by means of a modified HPLC method of Glare et al. [5] after solid-phase extraction with a Bond Elut C_8 extraction column (3 ml, 500 mg) (Varian, Harbor City, Calif., USA). The compounds were eluted from these columns with 3 ml of 2% (v/v) ammonia in methanol. Separation was obtained on an Alltima C_{18} 5 μm (250 × 4.6 mm) analytical column (Alltech, Deerfield, Ill., USA), protected by an Alltima C_{18} 5 μm (7.5 × 4 mm) guard column (Alltech). The mobile phase used consisted of 27.5% (v/v) acetonitrile in water containing 0.01 M sodium dihydrogen phosphate monohydrate and 0.001 M sodium dodecyl sulphate and was brought to pH 2.2 with phosphoric acid. The flow rate was set at 1 $ml \cdot min^{-1}$. Fluorescence detection was used with an excitation wavelength of 210 nm and an emission wavelength of 340 nm. For morphine (25 $ng \cdot ml^{-1}$, $n = 13$ and 300 $ng \cdot ml^{-1}$, $n = 15$), the interassay coefficients of variation were below 12% and mean analytical recoveries varied from 96% to 103%. For M-6-G (100 $ng \cdot ml^{-1}$, $n = 14$ and 2000 $ng \cdot ml^{-1}$, $n = 16$), the interassay coefficients of variation were below 12% and the mean analytical recoveries between 90% and 102%. For

Table 1 Patient characteristics

Patient	Gender, age (years)	Tumour site (metastases)	Morphine	
			Dose range (mg per day)	Duration (days)
GW	F, 66	Endometrium (brain and bone)	198	13
AR	M, 62	Caecum (brain and bone)	78–117	12
GL	M, 51	Kidney (lung and bone)	299–700	160[a]
GJ	M, 61	Scapula (–)	280–3000	37
LV	F, 57	Cervix (–)	140–980	89
NS	F, 53	Breast (bone)	156–445	37
EF	M, 50	Bladder (bone)	272–1050	8
AD	M, 58	Pancreas (liver)	60–583	24

[a] With an interruption from day 55 to day 70

M-3-G (500 ng·ml^{-1}, $n = 14$ and 10 000 ng·ml^{-1}, $n = 16$), the interassay coefficients of variation were below 14% and the mean analytical recoveries between 91% and 101%. The lower limits of quantification using 1 ml plasma were 5 ng·ml^{-1} for morphine, 20 ng·ml^{-1} for M-6-G and 50 ng·ml^{-1} for M-3-G. Extraction and injection of the concomitantly administered drugs onto the column, under the same chromatographic conditions, was carried out in order to exclude interference with the determination of morphine and its metabolites.

Calculations and analysis

To evaluate the content uniformity of the syringes, the concentrations of morphine in the freshly prepared solutions were compared with the prescribed concentrations. To study the stability and compatibility for each syringe, the differences between the initial concentrations of morphine and its degradation products and the concentrations after storage or use were calculated.

For each patient, the mean ratios of M-6-G and M-3-G to morphine were calculated. The plasma concentrations were also normalised to a dose of 1 mg per day. Interindividual variability was assessed by comparing the averages of the normalised plasma concentrations in each patient. The intraindividual variability of the plasma concentrations was assessed by visual inspection; moreover, for each patient the relative standard deviation of all normalised plasma concentrations and the ratio between the maximal and the minimal value obtained for these normalised concentrations during the study period were calculated. In order to evaluate a possible influence of dose or progression of illness for each patient, the mean of the normalised plasma concentrations was also calculated for each dose.

Results

Immediately after preparation, the solutions contained between 86.3% and 108.6% of the expected concentration of morphine; all solutions contained small amounts of pseudomorphine and morphine-*N*-oxide, but apomorphine was never found. During storage or infusion of the solutions, there was no decrease in morphine concentrations; the concentrations of morphine-*N*-oxide and pseudomorphine were often increased, but even then remained below 0.2% of the morphine concentrations.

In nearly all patients, slightly decreased concentrations of total protein (range 2.52–4.29 g·dl^{-1}) and albumin (range 4.61–7.73 g·dl^{-1}), and slightly to importantly increased concentrations of alpha-1-acid glycoprotein concentrations were found (range 48–378 mg·dl^{-1}). Plasma creatinine values were in the normal range (< 1.3 mg·dl^{-1}), except for patients GL, LV, NS and AD in whom, at one moment or another, creatinine values of 1.4, 1.6, 1.7 and 1.6, respectively, were found. In patient NS, gamma glutamyl transferase and aspartate aminotransferase concentrations increased during the study period to very high values (from 668 U·l^{-1} to 9491 U·l^{-1} and from 133 U·l^{-1} to 551 U·l^{-1}); in patients EF and AD, gamma glutamyl transferase values increased markedly over the study period (from 92 U·l^{-1} to 204 U·l^{-1} and from 246 U·l^{-1} to 552 U·l^{-1}).

The plasma concentrations of morphine and its active metabolite M-6-G in the eight patients are shown in Fig. 1. The plasma concentrations of the inactive metabolite M-3-G are not shown. The plasma concentrations of morphine ranged from 29 ng·ml^{-1} to 2051 ng·ml^{-1}, those of M-6-G from 72 ng·ml^{-1} to 4040 ng·ml^{-1} and those of M-3-G from 360 ng·ml^{-1} to 32 900 ng·ml^{-1}. The mean ratio of the plasma concentrations of M-6-G to morphine ranged in the eight patients from 2.2 to 4.5 while the mean ratio of the plasma concentrations of M-3-G to morphine ranged from 15.5 to 32.3. Table 2 shows the mean value, the residual standard deviation and the minimal/maximal ratio of the normalised plasma concentrations of morphine, M-6-G and M-3-G, calculated for each patient. It is apparent from Table 2 that there was important interindividual variability of morphine, M-6-G and M-3-G concentrations: the mean of the normalised plasma concentrations calculated for each patient ranged, in ng ml^{-1} mg^{-1}, from 0.3 to 0.8 for morphine, from 1.0 to 3.1 for M-6-G and from 6.8 to 24.3 for M-3-G. There was also important intraindividual variability: in all patients, the concentrations of morphine, M-6-G and M-3-G varied markedly during the days or weeks of infusion at a constant dose. The relative standard deviation of the mean normalised plasma concentrations was calculated for each patient: these values ranged from 26% to 56% for morphine, from 20% to 51% for M-6-G and from 20% to 49% for M-3-G (Table 2). The mean, normalised plasma concentrations of morphine and M-6-G for each dose level are shown for the eight patients in Fig. 2: there was no increase of these values with dose or time.

Discussion

The efficacy and the side effects of opioids such as morphine given for cancer pain vary considerably from patient to patient. This interindividual variability can be expected on the basis of pharmacokinetic and pharmacodynamic factors. There is, however, also a marked intraindividual variability in the responses to morphine, and it is not known to what extent pharmacokinetic factors can be responsible. Although chronic subcutaneous infusions of morphine are extensively used in cancer patients, only scarce pharmacokinetic data are available for this route of administration [6, 7]. We therefore measured the plasma concentrations of morphine and its glucuronides in a series of such patients.

No loss of active substance in the solutions due to storage or addition of other drugs was observed. Two degradation products, pseudomorphine and morphine-*N*-oxide, were already present in the freshly prepared solutions and increased during storage, but remained below 0.2% of the morphine concentration. Hung et al. [8] also found pseudomorphine in freshly prepared solutions, but morphine-*N*-oxide was not determined in that study.

For the determination of morphine and its glucuronides in plasma, a HPLC method of adequate quality was used. None of the concomitantly given medications

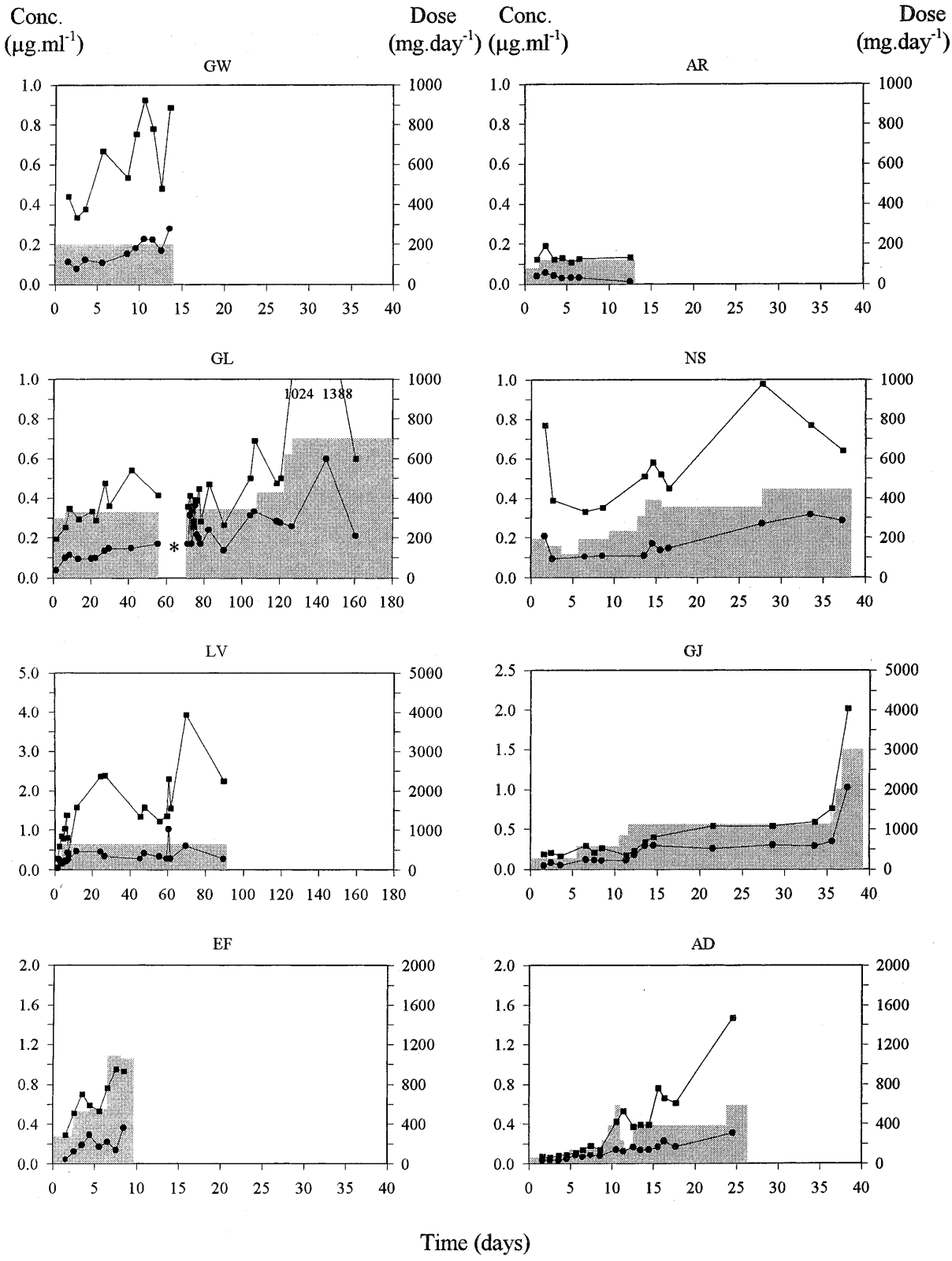

Fig. 1 Plasma concentrations of morphine (●) and morphine-6-glucuronide (■) and daily doses of morphine in eight terminally ill patients receiving a subcutaneous infusion of morphine. The daily doses are indicated by the *shaded area*. *In patient GL, the subcutaneous infusion was interrupted from day 55 to day 70

interfered with the determination of morphine and its glucuronides, but interference of metabolites cannot be excluded. The plasma concentrations of morphine and the ratios of the plasma concentrations of M-6-G and M-3-G to morphine were in the range reported in the

Table 2 Mean residual standard deviation (RSD) and maximal/minimal ratio of the normalised plasma concentrations of morphine, morphine-6-glucuronide (*M-6-G*) and morphine-3-glucuronide (*M-3-G*) calculated for each patient. *n* number of samples used for the calculation

Patient	*n*	Morphine			M-6-G			M-3-G		
		Mean ($ng \cdot ml^{-1} \cdot mg^{-1}$)	RSD (%)	Max/Min	Mean ($ng \cdot ml^{-1} \cdot mg^{-1}$)	RSD (%)	Max/Min	Mean ($ng \cdot ml^{-1} \cdot mg^{-1}$)	RSD (%)	Max/Min
GW	10	0.83	38	3.62	3.12	35	2.77	24.3	35	2.68
AR	6	0.41	48	3.01	1.37	42	2.63	10.5	43	2.70
GL	27	0.52	37	3.37	1.12	29	2.72	8.17	29	3.31
GJ	15	0.46	26	2.58	0.97	35	3.55	6.83	31	3.16
LV	18	0.55	56	6.80	2.46	51	13.6	15.9	49	11.5
NS	11	0.58	37	3.07	1.96	41	3.13	16.4	35	2.60
EF	8	0.33	42	1.33	1.14	20	1.67	9.08	20	1.74
AD	17	0.52	33	4.40	1.38	42	3.50	10.7	42	4.00

Fig. 2 Mean normalised plasma concentrations of morphine, morphine-6-glucuronide (*M-6-G*) and morphine-3-glucuronide (*M-3-G*) in eight terminally ill patients receiving a subcutaneous infusion of morphine. Each *column* represents the mean normalised plasma concentration for a given dose level (for dose levels see Fig. 1)

literature during short-term subcutaneous infusion of morphine [6, 7]. Comparison of the normalised plasma concentrations in the different patients revealed extensive interindividual variability, as much for morphine as for its metabolites. Visual inspection of the plasma concentrations at different sampling points for the same infusion rate in each patient (Fig. 1) revealed important intraindividual variability, which was confirmed when the plasma concentrations were normalised for dose. From Fig. 2, it is also obvious that the fluctuations of M-6-G and M-3-G concentrations with time were parallel.

There are no obvious explanations for the large intraindividual variability we have observed. We could not find any relationship with factors such as the hour of sampling, the site of the needle insertion, addition of other drugs to the syringe or prolonged infusion at the same site. The normalised plasma concentrations did not suggest non-linearity related to dose, thus confirming the findings of Säwe et al. [9]. Normalised plasma concentrations of morphine did not increase, even in the very late stages of the disease. There were no patient characteristics which could be related to this variability. In view of the low binding to plasma proteins [10], it is not likely that changes in binding due to altered plasma protein concentrations, for example, would explain the variability. In four of the patients, slightly increased creatinine values were found; however, no increased ratio of M-6-G or M-3-G to morphine was seen. In three patients, the hepatic enzymes were elevated: these patients did not show higher concentrations of morphine. Data from the literature about the influence of liver disease on morphine kinetics are conflicting [11].

The patients received multiple other drugs, mainly corticosteroids and laxatives. None of these concomitantly given drugs is known to cause major interactions with the glucuronidation process, which is the major metabolic pathway for morphine. We are left with factors which are difficult to ascertain. Absorption from the subcutaneous site, for example, could be responsible. In patient GL, hard discs which lasted for weeks were found at the site of infusion, but the concentrations of morphine and its glucuronides in this patient were not lower than those in other patients. Addition of hyalase to the morphine solution did not prevent the disc formation and did not lead to an increase of the morphine concentrations. Morphine is a high-extraction drug, and its clearance is mainly determined by the hepatic blood flow which is influenced by factors such as posture, ingestion of food and time of day [12]. These factors could be responsible for the variability observed. That the intraindividual variation of the ratio M-3-G to M-6-G was smaller than that of the ratio of either M-3-G or M-6-G to morphine is compatible with a role of hepatic blood flow variations.

In conclusion, during subcutaneous infusion of morphine, there is broad intra- and interindividual variability of the plasma concentrations of morphine and its glucuronides. The fluctuations in pain control and in adverse effects of morphine were not measured. It is, therefore, not possible to speculate upon the possible clinical relevance of these findings. If any attempt is made to correlate clinical events with plasma concentrations, one will have to take into account that effects depend upon both morphine and M-6-G concentrations, and that M-3-G could act as an opioid antagonist.

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