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MORPHINE METABOLISM IN CANCER PATIENTS ON INCREASING ORAL DOSES—NO EVIDENCE FOR AUTOINDUCTION OR DOSE-DEPENDENCE

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1 Four cancer patients with severe chronic pain were treated with oral morphine with increasing doses during 5–8 months. During this period the oral dose was increased 16–23-fold in each of the patients. Morphine, morphine-3- and morphine-6-glucuronide were determined with high performance liquid chromatography in plasma and urine during steady-state, at five or more occasions on different daily doses of morphine.

2 The trough concentrations of morphine and its metabolites were linearly related to the given dose. The relation between the levels of morphine and the two glucuronides was constant in the individual patient and independent of dose and duration of treatment. The average molar ratio between the areas under the plasma concentration-time curves (AUC) for morphine-3-glucuronide and morphine was 34.0 (range 23.0–46.9). The corresponding value for the ratio between morphine-6-glucuronide and morphine was 3.9 (range 2.7–5.6).

3 Our results show that the conjugation of morphine with glucuronic acid is proportional to the dose during long-term treatment with increasing doses, thus this metabolic pathway is not subject to auto-induction, even after very long periods of continuous treatment with high doses.

Keywords morphine metabolism cancer patients autoinduction dose-dependence

Introduction

Oral morphine administered at regular dose intervals for long periods of time is now increasingly used in the treatment of cancer pain. Clinical experience suggests that development of tolerance does not lead to therapeutic failures. After the initial phase most patients are stabilized on a constant dose level and show no tendency to increase the dose (Twycross & Wald, 1976). However, in some patients it is necessary to increase the dose due to increased pain attributable to progress of the disease and/or development of tolerance.

The biochemical changes that underlie the development of tolerance are not yet understood. Several investigators have searched for a metabolic correlate to the development of tolerance to the pharmacological effects (Axelrod, 1956; Mellet & Wood, 1956; Johannesson & Shou, 1963; Mulé & Wood, 1962). In these studies it was shown that morphine glucuronidation, which is the major metabolic pathway, does not differ between nontolerant and tolerant animals, whilst *N*-demethylation, a minor pathway has been reported to be decreased as a result of treatment with morphine or other opiates. These findings indicate that alterations in the metabolism of the drug are too small to account for the development of tolerance. It is now well recognized that tolerance is largely due to altered drug response in the neural tissue and it has been suggested that it does not reflect a change at the receptor level but in some of the subsequent processes (Herz *et al.*, 1980).

To our knowledge there are no comparative prospective studies of the plasma kinetics of morphine and its metabolites in man at different dose levels during long-term treatment. The studies which hitherto have been published comprise only urinary data. The total amount of morphine and conjugated and unconjugated metabolites excreted in urine was found to account for about 85% of the dose during chronic morphine administration (Yeh, 1975). No comparison was however made with the excretion pattern in opiate naive subjects. In accordance with the animal studies mentioned above a decreased *N*-demethylation of morphine was demonstrated by Hahn *et al.* (1977) on the basis of urinary excretion data from one normal subject and one opiate addict.

The purpose of the present study was to evaluate the effects of long-term treatment and dose escalations on the metabolism of morphine. We will describe the plasma kinetics of morphine and its 3- and 6-glucuronidated metabolites at different times

during long-term treatment of cancer patients with increasing doses of morphine.

Methods

Four patients, two males (KS, IW) and two females (RS, MS) with carcinoma of the lung were investigated. Their ages ranged between 59 and 65 years. They all suffered from chronic intractable pain in the thoracic region attributable to their disease. Due to progress of the disease there was a continuous decrease in body weight throughout the study period. The clinical condition of the patients was however, relatively good, with a performance status of 70% or higher (100–80: Able to carry on normal activity; no special care needed. 70–50: Unable to work; can live at home; can care for most personal needs; varying amount of help needed. 40–0: Cannot care for self; needs institutional or hospital care or equivalent; disease may be rapidly progressive) according to Karnowsky *et al.* (1948). Except for shorter periods, all patients were able to stay at home without medical assistance. Regular visits at the out-patient clinic were made approximately every fortnight. Since the study was extended over several months it was impossible to exclude some other drugs (Table 1). The clinical data of the patients are shown in Table 1. Informed consent was obtained from all patients before the study, which was approved by the Ethics Committee of the hospital.

The oral morphine mixture contained an individualized amount of morphine hydrochloride (corresponding to 25–420 mg morphine base), 2.5 g (96%) ethyl alcohol, 7 g syrupus ribis nigri and aqua purificata to a total volume of 20 ml. The volume of each dose was kept constant at 20 ml, whilst the amount of morphine was changed when there was a need for dose adjustment. The morphine dose was administered at regular intervals every third or fourth hour. The patient's pain was regularly evaluated throughout the whole treatment period and dose adjustments were done when necessary. The dose and/or dose intervals were hence individualized according to the patient's need.

Blood samples were collected repeatedly during the study at different dose levels. Plasma samples were drawn prior to the administration of the dose. In two of the patients (KS and IW) blood samples were also drawn during the dose interval: before and 20, 40, 60, 120, 180 and 240 min after the dose was administered. Urine was also collected during the dose intervals in patient IW. Food intake was not allowed 2–3 h before or after the dose was given. The patient remained in a supine position for approximately 3 h after morphine was administered.

In order to achieve steady-state the studies were peformed at least 3 days after the latest dose adjustment since the half-life of morphine varies between 1 and 7 h (Säwe *et al.*, 1981). Blood samples were drawn into heparinized plastic tubes and immediately centrifuged at 900 *g*. The plasma and urine samples were stored at −20°C until analysed.

Morphine, morphine-3- and morphine-6-glucuronide in plasma and urine samples were determined with reversed phase high performance liquid chromatography (h.p.l.c.) with ion-pair formation, using 1-dodecyl sulphate as counter ion (Svensson *et al.*, 1982).

Results

During the observation period which extended over 5–8 months there was a 16–23 fold increase of the oral dose of morphine. The escalations of the dose over time for the individual patients are shown in Figure 1. The total daily dose ranged between 80 and 2520 mg. The dosage intervals were 4 h in patients IW, RS and MS and 3 h in patient KS. The plasma kinetics of morphine and its metabolites were studied at five to eight different dose levels in each of the patients (Figure 1).

Single plasma samples before dose

The plasma concentrations of morphine before the dose was administered varied between 0.06 and 1.64 μmol/l in the four patients. As seen in Figure 2a there was a linear relation between the daily dose and the trough concentration of morphine in plasma. There were, however, pronounced interindividual differences in the disposition of morphine.

The corresponding concentrations of the two metabolites, morphine-3- and morphine-6-glucuronide were considerably higher than the morphine concentrations. The concentrations of morphine-3-glucuronide varied between 1.71 and 28.2 μmol/l and those of morphine-6-glucuronide between 0.25 and 3.54 μmol/l. The trough concentrations in plasma of the two glucuronides were also linearly related to the daily dose of oral morphine. However, as evident from Figure 2 (b,c) which depicts the relation between the daily dose and the trough concentration of the glucuronides there were less pronounced differences between the patients in the concentrations of the two glucuronides as compared to corresponding morphine concentrations.

Dose interval study

In patients KS and IW samples were collected during the whole dose intervals. The plasma concentration *vs* time curves for morphine, morphine–3 and morphine-6-glucuronide at different times during the

Table 1 The clinical data of the four cancer patients in the study

Patient	*Age (years)*	*Sex*	*Weight (kg)*	*Location of the tumour (histopathological diagnosis)*	*Relevant clinical and laboratory findings*	*Concurrent medication (Daily dose and *date of start of therapy)*	*Date of start of morphine treatment*
RS	65	F	43	Lung (Adenocarcinoma)	No kidney or hepatic dysfunction	None	7 Feb
KS	64	M	59	Lung (Epidermoid)	No kidney or hepatic dysfunction	Paracetamol 3–6 g Pentobarbitone 100 mg Nitrazepam 10 mg	25 Dec
IW	59	M	67	Lung (Anaplastic)	Slight dependent oedema No kidney or hepatic dysfunction Bone metastases	Paracetamol 3–6 g Thioridazine 50 mg Oxazepam 30–75 mg (5 Feb) Theophylline 600 mg (19 Feb) Frusemide 40 mg (24 May) Chlorzoxazone 125 mg Acetylsalicylic acid 500 mg ** Dextropropoxyphene 45 mg Penicillin (23 June) Cytotoxic drugs (+ prednisolone) Treatment periods: 27 Feb 17 March 21 April 26 May 25 June	12 Jan
MS	62	F	47	Lung (Adenocarcinoma)	Periarthrial oedema Pleural metastases Pleurafluid No kidney or hepatic dysfunction	Frusemide 40 mg (1 Oct) Potassium 0.75 g (1 Oct) Acetylsalicylic acid 3 g (3 Dec) Chlorpromazine 75 mg (27 Dec)	21 Sept

* (No date indicates that therapy started before the actual study)
** (Fixed combination. *Ad libitum* 2–6 tablets day)

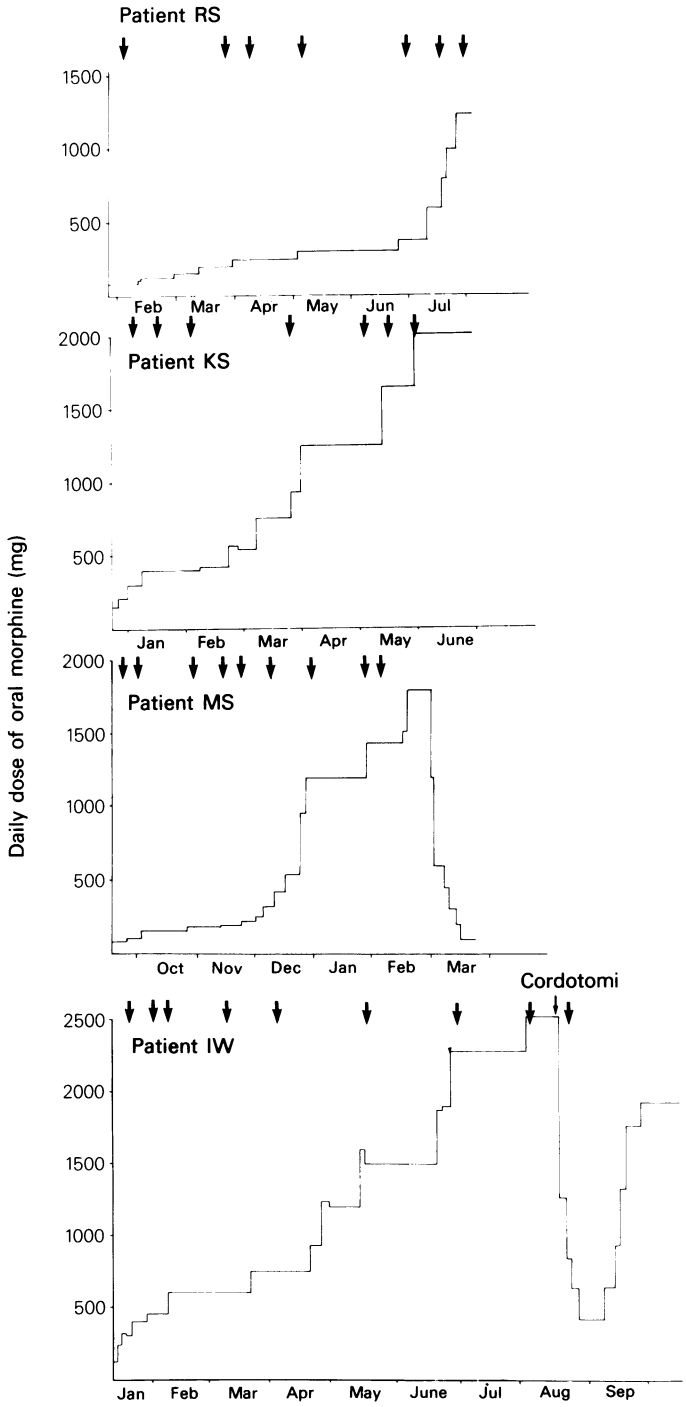

Figure 1 The increase of the daily dose of oral morphine in four cancer patients (the arrows indicate sampling periods).

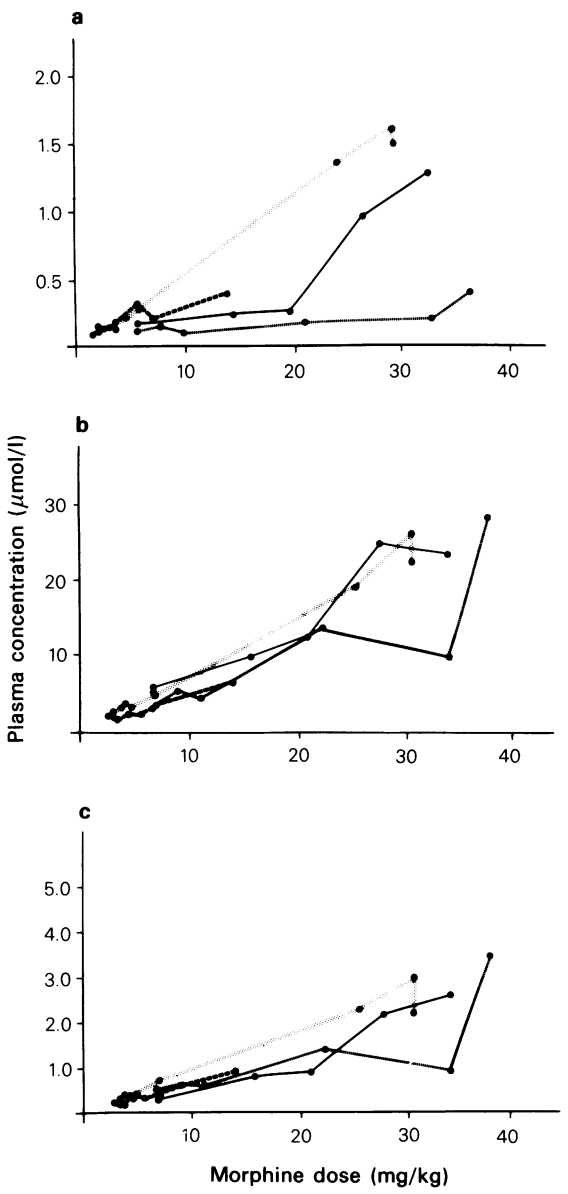

Figure 2 The relation between the trough concentrations of morphine (**a**), morphine-3- (**b**) and morphine-6-glucuronide (**c**) and the daily dose of oral morphine in four cancer patients.

treatment period are shown in Figure 3 for one of the patients (IW).

The areas under the plasma concentration *vs* time curves (AUC) for morphine and the metabolites were linearly related to the daily dose (Figure 4). The estimates of the AUC were reproducible on the same dose level. This is demonstrated in e.g. patient KS in whom the AUC was fairly constant within a period of 3 weeks at a dose level of 400 mg/day (Figure 4a).

The relation between morphine and the two glucuronides remained constant during the treatment period with increasing doses. The average morphine-3-glucuronide/morphine AUC ratio was 34.0 with a range from 23.0 to 46.9, whilst the corresponding value for morphine-6-glucuronide was 3.9 (2.7–5.6). The ratio of morphine-3-glucuronide/morphine-6-glucuronide varied between 6.7 and 14.3 (mean 9.0). The data in Table 2 show that the ratios were relatively constant within the patient irrespective of dose and duration of treatment.

In patient IW the concentrations of morphine and its metabolites were also determined in urine collected during a dosage interval at six different dose levels. As was the case for the metabolite/morphine ratios in plasma, the corresponding ratios in urine were also fairly constant and did not show any deviating trends during the treatment period (Figure 5). The recovery of the dose on the five different dose levels ranged between 39 and 71.4%.

Discussion

This study shows that the conjugation of morphine with glucuronic acid is proportional to the dose during long-term treatment with increasing doses, i.e. this metabolic pathway is neither subject to auto-induction nor saturation, even after very long periods of continuous treatment with increasing doses. This is evident from the linear relation between the dose and the plasma levels of morphine as well as its 3- and 6-glucuronidated metabolites. In addition, there was no change during the treatment period in the ratio between morphine and its two glucuronidated metabolites nor between the two glucuronides. A constant ratio between morphine and the glucuronides was observed both in plasma and in urine. Thus, our results indicate that the glucuronidation capacity for the individual patient is fairly constant and has a high capacity. Neither exogenous and endogenous factors nor the debilitating disease itself seem to interfere with the glucuronidation during several months of therapy. This is supported by the fact that a 75% decrease of the dose in patient IW after 8 months' therapy resulted in a corresponding decrease of the plasma concentrations of morphine, morphine-3- and morphine-6-glucuronide. At this time the AUC was

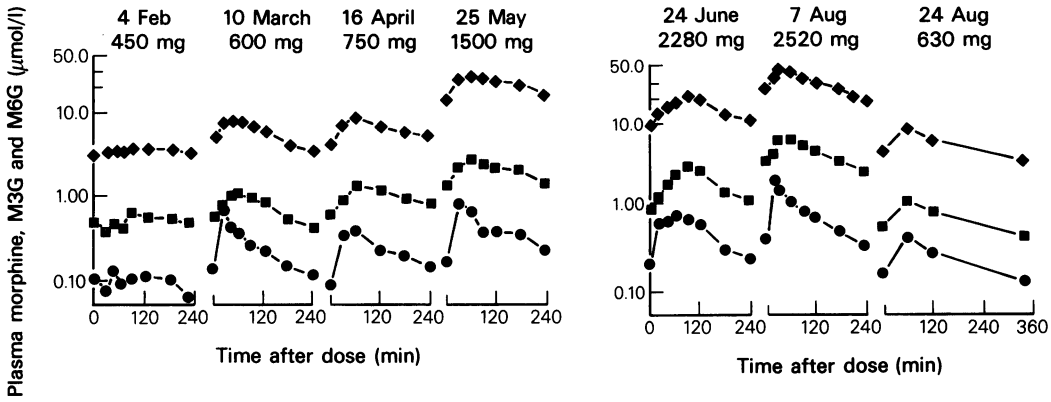

Figure 3 Concentration *vs* time curves for morphine (●), morphine-3- (◆) and morphine-6-glucuronide (■) at different occasions during the treatment period in one of the patients (patient IW).

similar to the AUC measured at the same dose level 5 months earlier (Figure 4b).

Our *in vivo* results show that patients have a high capacity to glucuronidate gram quantities of morphine. The present data are consistent with *in vitro* data with other drugs where the glucuronidation pathway has a high capacity as compared to e.g. sulphate conjugation (Moldéus, 1978).

In cancer patients there are many factors that theoretically might perturb the activity of UDP-glucuronyltransferase e.g. catabolism, cytotoxic drugs or other concurrent medication. Protein deficiency has been reported to raise the UDP-glucuronyltransferase activity (Wood & Woodcock, 1977). Phenobarbitone and 3-methylcholanthrene are known inducers of this enzyme (Bock, 1974). Our data and those of others seem to indicate that drug tolerance *per se* is not associated with changes in UDP-glucuronyltransferase activity. Whereas development of morphine tolerance was not associated with a change in UDP-glucuronyltransferase activity towards *p*-nitrophenol, increased UDP-glucuronyltransferase activity towards oestradiol was observed (Heath & Dingell, 1974). In rats UDP-glucuronyltransferase activity with 4-hydroxyamphetamine as substrate was not induced by amphetamine treatment nor was it increased in tolerant animals (Dingell *et al.*, 1974).

In light of the *pharmacodynamic* tolerance to large intravenous doses of morphine seen in addicts it is not plausible that *metabolic* tolerance would contribute to any great extent to the development of tolerance in man. The possible contribution of dispositional alterations during development of tolerance has, however, been discussed by several authors. In early studies in rats (Zauder, 1952; Takemori, 1960) it was claimed that the degree of morphine conjugation decreases in morphine tolerant rats as measured both *in vitro* and *in vivo*. These findings have not been confirmed in rats by other investigators (Axelrod, 1956; Abrams & Elliott, 1974). Studies in Rhesus monkeys (Mellet & Wood, 1956) have demonstrated only a trend towards decreased urinary excretion of total 'bound' morphine in opiate tolerant as compared to non-tolerant animals.

In contrast to the glucuronidation pathway the minor *N*-demethylation pathway seems to alter during development of opiate tolerance. Hahn *et al.* (1977) reported a lower urinary excretion of normorphine in one opiate dependent man compared to a normal male subject. These findings corroborate those of Axelrod (1956) who found that chronic administration of morphine led to a decreased *N*-demethylation of various opiates *in vitro* and *in vivo* in rats. Elison *et al.* (1964) have studied the *N*-demethylation *in vitro* in hepatic microsomes from tolerant and non-tolerant rats. They found that the K_m for the formation of normorphine was the same in the two groups but the V_{max} was lower in the tolerant rats. They speculated that the lower V_{max} could be due to lower concentrations of the enzyme as a consequence of decreased protein synthesis resulting from the chronic morphine administration. This possibility was, however, ruled out by Mannering & Takemori (1959).

Our high pressure liquid chromatographic method separates morphine, morphine-3-glucuronide, morphine-6-glucuronide, codeine as well as normorphine (Svensson *et al.*, 1982). However, absent or negligible plasma levels of normorphine in our patients precluded any assessment of the *N*-demethylation rate.

Interestingly, the disposition of morphine differed between the patients as evident from the different slopes of the regression lines for the steady-state concentration versus dose (Figure 2a). These findings are in agreement with our previous study of the kinetics of single doses of morphine in cancer patients that showed pronounced interindividual differences in the

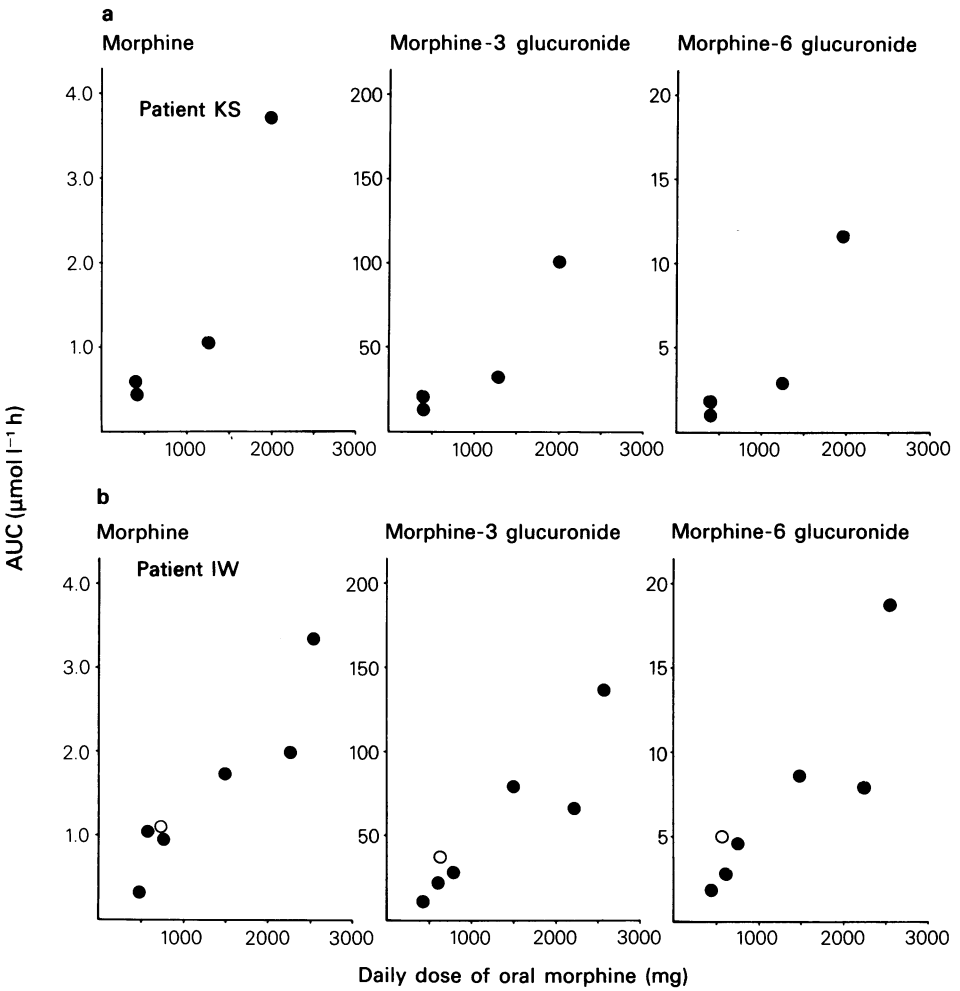

Figure 4 The relation between the AUCs of morphine, morphine-3- and morphine-6-glucuronide and the daily dose of oral morphine in patients KS (**a**) and IW (**b**). The dots indicate AUC-values obtained with 3 (patient KS) or 4 h dosing intervals (patient IW). The unfilled dot in patient IW indicates AUC during a 6 h dose interval. This value was obtained when the dose was decreased after 8 months of therapy.

Table 2 The relation between the AUC of morphine and the AUCs of the glucuronides at different doses of oral morphine during long-term treatment

Patient	*Date of treatment (days from start of therapy)*	*Daily dose (mg)*	*Plasma AUC* M3G / M*	*Plasma AUC* M3G / M6G*	*Plasma AUC* M6G / M*
IW	Feb 4 (24)	450	36.5	7.0	5.2
	March 10 (58)	600	23.0	8.1	2.8
	April 16 (95)	750	28.9	6.7	4.3
	May 25 (134)	1500	46.9	9.1	5.1
	June 24 (165)	2280	32.7	8.3	3.9
	Aug 7 (209)	2520	41.3	7.3	5.6
KS	Jan 19 (26)	400	41.5	14.4	2.9
	Feb 6 (44)	400	31.4	9.4	3.3
	April 24 (121)	930	—	—	—
	April 30 (128)	1240	31.0	11.5	2.7
	May 14 (142)	1640	—	—	—
	May 27 (155)	2000	27.1	8.6	3.1

* Area under the concentration *vs* time curves during a dose interval

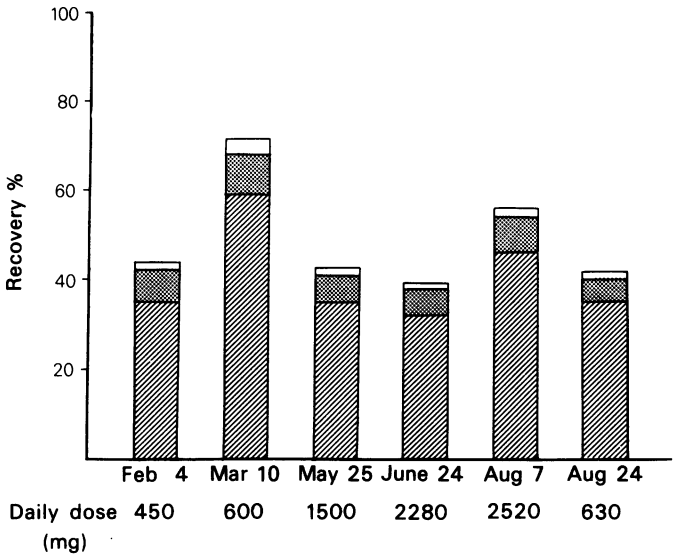

Figure 5 The recovery or morphine (□), morphine-3- (▨) and morphine-6-glucuronide (▩) in urine in patient IW.

plasma clearance and oral bioavailability (Säwe *et al.*, 1981).

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