Plasma levels of morphine and morphine glucuronides in the treatment of cancer pain: relationship to renal function and route of administration

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Summary. There is growing evidence that renally-impaired patients receiving morphine therapy are at greater risk of developing opiate toxicity, due to the accumulation of an active metabolite, morphine-6-glucuronide (M6G), which is usually excreted by the kidneys. This study examined the relationships between morphine dosage, renal function, and trough plasma concentrations of morphine and its glucuronide metabolites in 21 patients (aged mean: 68.5 years; 11 males) receiving either oral or subcutaneous morphine for terminal cancer pain. The median daily morphine dosages (mg·kg⁻¹) were: orally 1.87 (range 0.37–6.82) and subcutaneously 1.64 (range 0.22–3.60).

The median plasma concentrations of morphine, morphine-3-glucuronide (M3G), and M6G (ng·mL⁻¹) were: 36.0, 1035.2, and 142.3, respectively. The plasma concentrations of morphine, M3G and M6G were each significantly related to the daily morphine dosage (n = 21, Spearman r = 0.79, 0.91, and 0.88 respectively). Accumulation of the morphine glucuronides was dependent on renal function. The plasma concentrations of M3G and M6G, when divided by the morphine concentration, were significantly related to the calculated creatinine clearance of the patient. Patients receiving oral morphine had higher plasma concentration ratios of glucuronide/morphine than those receiving subcutaneous therapy, presumably due to first-pass glucuronidation.

The results of this study confirm that accumulation of the pharmacologically active M6G is related to renal function, which probably explains the observation that morphine dosage requirements are generally reduced in patients with renal impairment.

Key words: morphine, cancer; morphine-6-glucuronide, renal function, drug metabolism, pharmacokinetics

Morphine, administered either orally or parenterally, remains the analgesic drug of choice for the treatment of severe chronic pain in the terminally-ill patient (Walsh and West 1988). Patients vary considerably in their dosage requirements of morphine, so that the process of dosage individualisation is an important aspect in the clinical use of the drug. Much of this inter-patient variability is explained by large individual differences in the pharmacokinetics of morphine (Sawe 1986). For instance, Sawe (1984) and her co-workers (1981, 1985) reported large inter-subject ranges in each of the absorption (15–69% oral bioavailability), apparent volume of distribution (1.0–8.6 L·kg⁻¹) and elimination half-life (0.9–7.8 h) of morphine in a sample of 12 cancer patients.

Morphine is primarily eliminated by metabolism in the liver. Conjugation to morphine-3-glucuronide (M3G) accounts for over 50% of the administered morphine, while morphine-6-glucuronide (M6G) is a minor metabolite, accounting for about 5% (Sawe 1986; Chan and Matzke 1987). In cancer patients receiving oral morphine, steady-state plasma concentrations of M3G are approximately 20-fold, and M6G approximately 3-fold, higher than the morphine concentrations (Sawe 1986).

It has often been noted that morphine appears to produce an exaggerated clinical response in patients with renal disease (Chan and Matzke 1987). Indeed, it has been shown that the presence of renal impairment significantly reduces patients' dosage requirements of morphine (Regnard and Twycross 1984; Hoskin and Hanks 1988). Until recently, however, there was no satisfactory explanation for these observations since it was well known that the liver, not the kidney, is primarily responsible for the elimination of the drug. Then, Osborne et al. (1986) described three patients with renal failure who experienced pronounced respiratory depression following treatment with conventional dosages of morphine. Using a high performance liquid chromatographic (HPLC) assay (Svensson et al. 1982), they found that the patients had undetectable plasma levels of morphine, but very high levels of the two glucuronide metabolites. It had previously been shown that M6G is pharmacologically active, and may actually be more potent than morphine itself (Shimomura et al. 1971; Yoshimura et al. 1976; Abbott and Palmour 1988). Hence, the classical signs of morphine intoxication were attributed to the accumulation of M6G, which is usually
renally excreted. The elimination half-life of M6G ranged from 38–103 h. It was concluded that morphine does not accumulate in patients with renal disease but that accumulation of the glucuronide metabolites does occur, and this explains the increased sensitivity to morphine commonly observed in patients with renal impairment. It has recently been reported that a 1 mg intravenous dose of M6G produces analgesia lasting up to 7 h (Osborne et al. 1988).

Others have also shown that the elimination of the morphine glucuronides, but not of morphine, is significantly delayed following the administration of single morphine doses to subjects with renal disease (Sawe et al. 1985b; Woolner et al. 1986; Sawe and Odar-Cederlof 1987; Wolff et al. 1988; Sear et al. 1989). This is not altogether unexpected. The accumulation of glucuronide conjugates in patients with renal impairment has been previously reported with other drugs, including lorazepam, propranolol and clofibrate (Verbeeck 1982).

There are few data available on the plasma levels of the morphine glucuronides, in relation to renal function, in patients receiving chronic morphine therapy. The aim of this study was to gather such data.

**Methods**

In-patients at the Palliative Care Unit, Repatriation General Hospital, who were receiving chronic morphine therapy administered either as a four-hourly (03.00, 07.00, 11.00, 15.00, 19.00, and 23.00 h) oral aqueous solution before meals or subcutaneous infusion (via a Graseby® portable syringe pump) for cancer pain were consecutively selected for the study. Only patients receiving additional analgesic drugs were excluded.

Data were obtained from 21 patients, all terminally ill with cancer. The mean age of the sample was 68.5 (8.7) years (range 50–86 years), and 11 were males. Mean body weights were 67 (28) kg for the males and 59 (17) kg for the females. The patients were being treated with morphine via oral (14) or subcutaneous (7) routes for pain related to primary tumours at various sites, including the colon (6), upper respiratory tract (3), breast (2), stomach (2), prostate (2), and vagina (2). Seven of the patients also had active secondary tumours, generally bony metastases. The median duration of morphine therapy was 1 month (range 1 week–3 months). All patients were receiving several other drugs (median 6; range 2–13), including laxatives (18 patients), corticosteroids (12), anti-nauseants (12), hypnotics (11) and anti-fungals (4). None of the patients had clinical evidence of opioid-related toxicity.

After at least three days of therapy on a constant dosage, a blood sample was taken (pre-dose for oral therapy) and the plasma concentrations of morphine and its glucuronide metabolites promptly determined using the HPLC assay of Svensson et al. (1982). In our laboratory, the assay was reproducible with between- and within-day coefficients of variation below 7% for both morphine (60 ng · ml⁻¹) and M3G (600 ng · ml⁻¹), and mean recoveries in excess of 85%. The minimum detectable concentration of morphine and M3G in plasma was 5 ng · ml⁻¹. Whenever possible, blood was also drawn for the determination of serum creatinine and liver function tests, using standard methods on automatic analysers.

The creatinine clearance of most patients was estimated from sex, age, weight, and serum creatinine level, using the equation of Cockcroft and Gault (1976). The mean creatinine clearance was 60.9 (29.4) ml · min⁻¹ (n = 15; range 20.5–124.2 ml · min⁻¹). Patient age and estimated creatinine clearance were negatively correlated (r = −0.69, P < 0.001). Ten patients had biochemical evidence of liver disease (abnormal serum levels of at least two of bilirubin, aspartate aminotransaminase, alanine aminotransferase, alkaline phosphatase, or gamma glutamyl transpeptidase).

The oral and subcutaneous sub-groups of patients did not differ significantly with respect to patient age, estimated creatinine clearance, or morphine dosage. The median daily morphine dosages (mg · kg⁻¹) were: orally 1.87 (range 0.37–6.82) and subcutaneously 1.64 (range 0.22–3.60).

All results are expressed as mean (SD) unless otherwise stated. Statistical procedures used were least squares linear regression, Spearman rank correlations, Student’s t tests, and Mann Whitney U tests, as appropriate.

**Results**

The plasma concentrations of morphine and the morphine glucuronides all formed positively skewed distributions. The median values (ng · ml⁻¹) were: morphine 36.0