

# The influence of renal function on the renal clearance of morphine and its glucuronide metabolites in intensive-care patients

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- 1 The relationships between renal creatinine clearance and the renal clearances of morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) were studied in fifteen intensive-care patients who were receiving morphine sulphate by constant intravenous infusion and who had diverse renal function.
- 2 An arterial blood sample was collected before and after a 4–5 h urine collection. Plasma and urine concentrations of morphine, M3G and M6G were measured by h.p.l.c. Plasma binding of all three compounds in drug-free plasma from healthy volunteers was determined by ultrafiltration. Measured renal creatinine clearance ( $CL_{Cr, meas}$ ) was calculated from plasma and urinary creatinine concentrations (from h.p.l.c.). Also, creatinine clearance was predicted ( $CL_{Cr, pred}$ ) from routine laboratory determination of plasma creatinine (Jaffe method).
- 3 There were significant linear relationships ( $P < 0.001$ ) between  $CL_{Cr, meas}$  and the renal clearances of morphine, M3G and M6G. The unbound renal clearance of morphine exceeded  $CL_{Cr, meas}$  ( $P < 0.002$ ) while the unbound renal clearances of M3G and M6G did not differ from  $CL_{Cr, meas}$  ( $P > 0.5$ ).
- 4 In ten of the patients who received a constant infusion of morphine for at least 6 h, the dose-normalised plasma concentrations of M3G and M6G increased with decreasing  $CL_{Cr, pred}$ . Significant ( $P < 0.001$ ) relationships were observed between the reciprocal of  $CL_{Cr, pred}$  and the dose-normalised plasma concentrations of M3G and M6G.
- 5 The results indicate the importance of renal function in determining the renal clearances and plasma concentrations of M3G and M6G during intravenous infusion with morphine in intensive-care patients.

**Keywords** morphine glucuronide metabolites renal clearance  
plasma concentrations renal function

## Introduction

Morphine is used predominantly for the relief of post-operative and cancer pain. It is extensively metabolized in humans, primarily to morphine-3-glucuronide (M3G), with lesser amounts of morphine-6-glucuronide (M6G) and morphine-3-sulphate being formed (Yeh *et al.*, 1977).

Several workers have shown that M6G has analgesic activity in animals (Abbott & Palmour, 1988; Gong *et al.*, 1991; Pasternak *et al.*, 1987; Paul *et al.*, 1989; Shimomura *et al.*, 1971) and man (Osborne *et al.*, 1988), while

in animals M3G is without effect (Pasternak *et al.*, 1987; Shimomura *et al.*, 1971). However, M3G has been shown to counteract the analgesic activity of morphine and M6G in rats (Smith *et al.*, 1990; Watt *et al.*, 1990) and to stimulate ventilation in dogs (Pelligrino *et al.*, 1989) and rats (Gong *et al.*, 1991). Prolonged respiratory depression, following morphine administration to patients in renal failure, was attributed to the accumulation of M6G (Hasselström *et al.*, 1989; Osborne *et al.*, 1986).

The major route of elimination for M3G and M6G in subjects with normal renal function appears to be via renal excretion (Osborne *et al.*, 1990; Säwe, 1986). Data suggest that the elimination of M3G and M6G is influenced by renal function (Osborne *et al.*, 1988; Peterson *et al.*, 1990; Säwe & Odar-Cederlöf, 1987; Wolff *et al.*, 1988). In patients given morphine, the ratios of the plasma concentrations of M3G and M6G to that of morphine were found to increase as renal function decreased (Peterson *et al.*, 1990; Säwe, 1986). No studies to date have fully investigated the relationship between renal function and the renal clearance of the glucuronide metabolites. In view of the possible influence of these metabolites on the analgesic and adverse effects of morphine, a greater knowledge of this relationship may be of value in predicting the plasma concentrations of the glucuronides that are likely to be achieved when morphine is given to patients with diverse renal function.

The aims of the present study in intensive-care patients receiving morphine were: to determine the influence of renal function on the renal clearance of morphine, M3G and M6G; to gain an insight into the possible mechanisms of renal excretion of these compounds; and to determine whether clinical assessment of renal function allows one to predict the plasma concentrations of the glucuronides.

## Methods

### Patients

Fifteen patients in an intensive care unit, with diverse renal function, participated in the study. Demographic and clinical details for each patient are in Table 1. The study was approved by the Human Ethics Committee of the Royal Adelaide Hospital and the Committee on the Ethics of Human Experimentation of the University of Adelaide.

### Experimental design

Morphine sulphate B.P. was given by intravenous infusion for analgesia and sedation in doses ranging from 2 to 5 mg h<sup>-1</sup> (0.020 to 0.122 mg kg<sup>-1</sup> h<sup>-1</sup> morphine base), the dose having been determined on clinical grounds.

Two (5 ml) arterial blood samples were collected from each patient approximately 4 h apart, and the plasma separated by centrifugation. The bladder was emptied prior to collection of the first blood sample and then all urine produced was collected via a catheter up to the time of the next blood sample. The urine volume and

**Table 1** Demographic and clinical details of patients

Number	Sex	Age (years)	Weight (kg)	Duration morphine constant infusion	Diagnosis	Concomitant medication*
1	F	19	56	16d	Motor vehicle accident	1,2
2	F	20	60	29d	Viral pneumonia, pregnant 24/52	1,2,27
3	M	78	55	12.5h	Gastrointestinal bleeding, pulmonary oedema	3,4
4	F	61	55	3d	Pneumothorax, faecal peritonitis	3,5,6,7,27
5	M	72	64	6h	Axillo-bifemoral bypass	8,9,10,11,12,13
6	F	67	58	12h	Oesophago-gastrectomy	3,12,14
7	M	75	65	0h <sup>a</sup>	Ruptured aortic aneurysm	12,14,15,16,17,18,19,20
8	M	26	75	1h	Motor vehicle accident	21
9	M	74	70	6h	Partial cholecystectomy, pneumonia, alcoholic dementia, sub-dural haematoma	3,5,6,7,12,16,22
10	F	62	85	0.5h	Acute respiratory failure, pneumonia, breast cancer	7,12,23
11	M	57	70	4d	Acute respiratory distress syndrome, oesophageal stricture	3,7,12,18,23
12	M	23	65	2d	Metastatic aplastic carcinoma	7,8,11,20,22,24
13	M	62	70	3h	Aortic aneurysm	10,18,30
14	F	17	44	3.5h	Congenital heart disease	1,7,12,16,20,25,26
15	F	69	62	0h <sup>b</sup>	Septicaemia, pneumonia, acute renal failure	7,12,16,18,28,29

\*Key to concomitant medication: 1 = diazepam, 2 = vecuronium, 3 = midazolam, 4 = cefoxitin, 5 = gentamicin, 6 = metronidazole, 7 = salbutamol, 8 = paracetamol, 9 = temazepam, 10 = cephalothin, 11 = ranitidine, 12 = B group vitamins, 13 = Haemacell®, 14 = digoxin, 15 = folic acid, 16 = vitamin K, 17 = ascorbic acid, 18 = pancuronium, 19 = calcium chloride, 20 = frusemide, 21 = metoclopramide, 22 = amoxicillin, 23 = imipenem, 24 = hydrocortisone, 25 = nystatin, 26 = oxycodone, 27 = total parenteral nutrition, 28 = betamethasone cream, 29 = penicillin G, 30 = chlorpromazine.

<sup>a</sup> morphine infusion rate altered during the urine collection.

<sup>b</sup> morphine infusion ceased at the beginning of the urine collection.

pH were recorded. Plasma and aliquots of urine were stored at  $-20^{\circ}\text{C}$  prior to analysis.

#### Analytical techniques

The h.p.l.c. method of Milne *et al.* (1991), a modification of the original method of Svensson *et al.* (1982), was used to determine the concentrations of morphine, M3G and M6G in plasma and diluted urine. The minimum quantifiable concentrations (coefficients of variation  $< 10\%$ ) in plasma were  $13.3\text{ nmol l}^{-1}$ ,  $108\text{ nmol l}^{-1}$  and  $41\text{ nmol l}^{-1}$  for morphine, M3G and M6G, respectively. One  $\text{nmol l}^{-1}$  is equivalent to  $0.29\text{ ng ml}^{-1}$  of morphine and  $0.46\text{ ng ml}^{-1}$  of the glucuronides.

Creatinine in plasma and urine was determined by a modification of the h.p.l.c. method of Huang & Chiou (1983). Briefly,  $0.1\text{ ml}$  plasma was mixed with  $0.25\text{ ml}$  acetonitrile, centrifuged, and  $30\text{ }\mu\text{l}$  of the supernate was injected onto the column;  $0.05\text{ ml}$  urine was mixed with  $2\text{ ml } 10\%$  v/v acetonitrile in water and  $25\text{ }\mu\text{l}$  was injected onto a column packed with Partisil-10 SCX (Whatman Chemical Separation, Inc., Clifton, NJ, USA). The mobile phase,  $10\%$  v/v acetonitrile in  $0.02\text{ mol l}^{-1}$  ammonium dihydrogen phosphate buffer (pH 4.8), was pumped at  $1.5\text{ ml min}^{-1}$ .

The plasma creatinine concentration was also obtained from the patients' records, having been determined in a separate plasma sample from blood collected on the day of the study for routine biochemical analyses. The creatinine concentration was determined by the Jaffe method, as modified for automated analysis (SMAC II, Technicon Corporation, Tarrytown, NJ, USA).

#### Plasma binding studies

Plasma from five healthy volunteers (age 25 to 39 years), spiked with morphine ( $266\text{ nmol l}^{-1}$ ), M3G ( $2170\text{ nmol l}^{-1}$ ) and M6G ( $1020\text{ nmol l}^{-1}$ ), was subjected to ultrafiltration at  $37^{\circ}\text{C}$  using an MPS-1 apparatus fitted with a YMT membrane (Amicon Corp., Danvers, MA, USA). The concentrations of morphine, M3G and M6G in aliquots of filtrate ( $0.5\text{ ml}$ ) and plasma ( $1.0\text{ ml}$ ), determined by h.p.l.c., were used to calculate the fraction unbound in plasma. Preliminary experiments indicated there was no binding of morphine, M3G or M6G to the ultrafiltration apparatus.

#### Data analysis

For all patients, the renal clearances of morphine, M3G and M6G were calculated as the respective urinary excretion rate divided by the mean of the two plasma concentrations spanning the urine collection interval.

For the 10 patients with an infusion rate that was constant for at least 6 h before the first blood sample, the plasma clearance of morphine was calculated as infusion rate divided by the mean plasma concentration. In addition, for the same ten patients, the recovery of the dose in urine as morphine, M3G and M6G was calculated from the amount excreted as each compound divided by the morphine dose (expressed in molar terms) during the time of urine collection.

The plasma concentration ratios for M3G/M, M6G/M and M3G/M6G in each patient were calculated from the

mean of the plasma concentrations of the glucuronides and morphine determined in the two samples.

Measured renal creatinine clearance ( $\text{CL}_{\text{Cr, meas}}$ ), as a marker of renal function, was calculated as the urinary excretion rate divided by the creatinine concentration from the first plasma sample, the plasma and urine concentrations of creatinine having been determined by h.p.l.c. In addition, predicted creatinine clearance ( $\text{CL}_{\text{Cr, pred}}$ ), was calculated from the formula based on age, sex, body weight and plasma creatinine concentration obtained from the patients' records (Cockcroft & Gault, 1976).

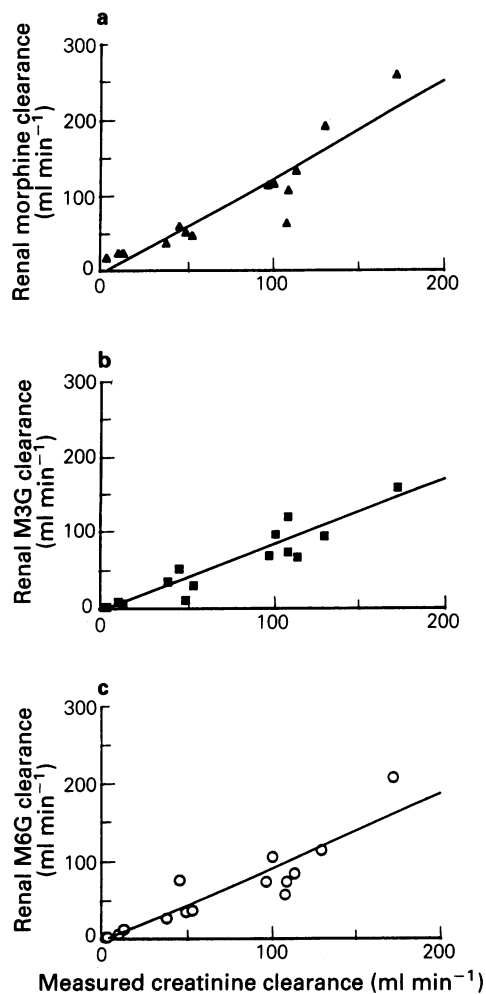
Possible relationships between variables were examined by simple or multiple linear regression; associations were examined by Spearman Rank analysis. Comparisons of means between two or more variables were performed using Student's *t*-test or one-way analysis of variance. *A posteriori* comparisons were performed using the Scheffé *F*-test. *P* less than 0.05 was considered significant.

#### Results

The mean of the two plasma concentrations of morphine, M3G and M6G achieved in the individual patients ranged from  $0.048$  to  $0.33\text{ }\mu\text{mol l}^{-1}$ ,  $0.31$  to  $37\text{ }\mu\text{mol l}^{-1}$  and  $0.093$  to  $11\text{ }\mu\text{mol l}^{-1}$ , respectively. During the urine collection interval, the change in plasma concentrations of morphine (calculated for each patient as the difference divided by the mean of the two values and multiplied by 100) in 10 patients who received morphine at a constant infusion rate for at least 6 h ranged from  $-31\%$  to  $+45\%$ , while in four of the patients where the infusion rate had been altered within 6 h prior to the first blood sample the change in plasma morphine concentrations ranged from  $-59\%$  to  $+36\%$ . For these fourteen patients, the plasma concentration ratios of M3G/morphine and M6G/morphine ranged from 4.0 to 170 and 0.79 to 51, respectively. Plasma concentration values of morphine in patient 7 were excluded because of a change in the infusion rate of morphine between collection of the two plasma samples. Considering all fifteen patients, the change in plasma concentrations of M3G and M6G ranged from  $-23\%$  to  $+27\%$  and  $-24\%$  to  $+27\%$ , respectively. The mean ( $\pm$  s.e. mean,  $n = 15$ ) plasma concentration ratio of M3G/M6G was  $5.0 \pm 0.3$ . For patient 7, the plasma concentrations of M3G and M6G differed by only 22% and 12%, respectively, between the first and second samples and hence the data for the glucuronides from this patient were included.

The renal clearance of creatinine ( $\text{CL}_{\text{Cr, meas}}$ ) ranged from  $2.5$  to  $170\text{ ml min}^{-1}$ . There were significant linear relationships between the plasma creatinine concentrations ( $\text{mmol l}^{-1}$ ) determined by the modified Jaffe and h.p.l.c. methods (Jaffe =  $1.14\text{ h.p.l.c.} + 0.002$ ,  $r = 0.983$ , 14 df,  $P < 0.001$ ), and between  $\text{CL}_{\text{Cr, pred}}$  and  $\text{CL}_{\text{Cr, meas}}$  ( $\text{CL}_{\text{Cr, pred}} = 0.686\text{ CL}_{\text{Cr, meas}} + 26.3$ ,  $r = 0.763$ , 14 df,  $P < 0.001$ ). Exclusion of the three patients receiving cephalosporins (which may interfere with the Jaffe method) did not alter substantially the regression between the two methods for plasma creatinine determination.

There were significant linear relationships between

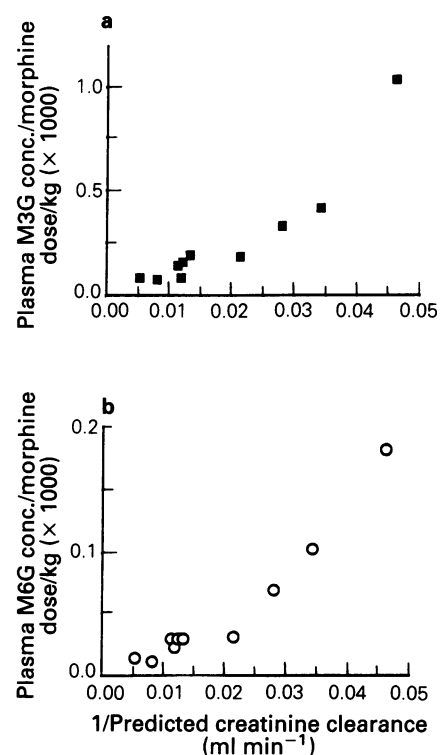


**Figure 1** The relationship between renal function, assessed by measured renal creatinine clearance, and the renal clearance of a) morphine ( $y = 1.28x - 5.81$ ,  $r = 0.926$ , 13 df,  $P < 0.001$ ), b) M3G ( $y = 0.86x - 3.85$ ,  $r = 0.943$ , 14 df,  $P < 0.001$ ) and c) M6G ( $y = 0.97x - 6.51$ ,  $r = 0.910$ , 14 df,  $P < 0.001$ ).

the renal clearances of either morphine, M3G or M6G and  $CL_{Cr, meas}$  ( $r \geq 0.910$ ,  $P < 0.001$ , Figure 1). The 95% confidence interval for the slope of the regression line was 0.95–1.61, 0.68–1.04 and 0.70–1.23 for morphine, M3G and M6G, respectively. There was no improvement when, using multiple regression analysis, the additional influence of urine flow rate or pH was considered for each compound. The renal clearance of morphine was significantly ( $P < 0.001$ ) greater than the renal clearance of either glucuronide. There was no difference ( $P > 0.5$ ) in renal clearance between the glucuronides.

The mean ( $\pm$  s.e. mean) fraction unbound for morphine, M3G and M6G in the plasma from five healthy volunteers was  $0.74 \pm 0.01$ ,  $0.85 \pm 0.02$  and  $0.89 \pm 0.02$ , respectively. When these values were used to calculate the unbound renal clearances of morphine, M3G and M6G, the slope of the regression line for unbound renal clearance of morphine against  $CL_{Cr, meas}$  was significantly greater than unity ( $P < 0.002$ ); similar regression analyses for M3G and M6G revealed slopes not different from unity ( $P > 0.5$ ).

Ten of the patients were maintained on a fixed infusion rate for at least 6 h, and for the two who received a constant infusion for 6 h only, the change in plasma



**Figure 2** Spearman Rank analysis of the association between dose rate/kg-normalized plasma concentration of a) M3G ( $P < 0.001$ ) and b) M6G ( $P < 0.001$ ) and the reciprocal of creatinine clearance predicted from the Cockcroft-Gault formula.

morphine concentration between the first and second sample was +17% and +35%. In this group of 10 patients, the plasma clearance of morphine ranged from 5.6 to 30.6 ml min<sup>-1</sup> kg<sup>-1</sup> (mean  $\pm$  s.e. mean:  $17.5 \pm 2.9$  ml min<sup>-1</sup> kg<sup>-1</sup>). There was no significant difference ( $P > 0.35$ ) in the mean plasma clearance of the five patients infused at a constant rate for between 6 and 24 h and the five infused for longer than 24 h. Total recovery of the morphine dose in urine as the sum of morphine, M3G and M6G ranged from 26% to 129% and was not related to  $CL_{Cr, meas}$ . Individual recoveries of morphine, M3G and M6G ranged from 1.3% to 17%, 20% to 99% and 3.4% to 19%, respectively.

For the ten patients who received a constant infusion for at least 6 h, Figure 2 shows the relationships between the plasma concentrations of M3G and M6G, normalized for molar dose rate of morphine per kg bodyweight, and  $1/CL_{Cr, pred}$ . Spearman Rank analysis revealed these to be significant associations ( $P < 0.001$ ).

## Discussion

Previous pharmacokinetic studies have been performed during continuous intravenous infusion with morphine in postoperative patients with apparently normal hepatic and renal functions (Persson *et al.*, 1986; Tanguy *et al.*, 1987). After correcting for the morphine blood/plasma concentration ratio of 1.1 determined in humans (Patwardhan *et al.*, 1981), the plasma clearance values found in the present study are similar in distribution to the blood clearance values reported by Persson *et al.*

(1986). However, they are approximately half the values reported by Tanguy *et al.* (1987). The patients included in the present study had varying degrees of renal function but no overt hepatic dysfunction. Those included in the calculation for plasma morphine clearance had been infused at a constant rate for between 6 h and 29 days and it is possible that steady-state concentrations of morphine may not have been achieved in the patients infused for the shorter periods. However, there was no difference in estimated plasma clearance between the patients infused from 6 h to 24 h and those infused for greater than 24 h.

There have been no previous reports on the plasma concentrations of M3G and M6G achieved during continuous intravenous infusion with morphine. The ratios of the plasma concentrations of M3G/morphine and M6G/morphine approximated those found previously in cancer patients infused subcutaneously with morphine (Peterson *et al.*, 1990; unpublished observations). The wide range in ratios reflects the extremes of renal function in the patients and was not unexpected, since the glucuronides are cleared primarily by urinary excretion, while morphine is cleared principally by metabolism. The consistency in the M3G/M6G plasma concentration ratio between patients and the similarity in renal clearances of the glucuronides within patients suggests a consistency between patients in the relative metabolic formation clearance of both compounds from the parent morphine.

The mean ( $\pm$  s.e. mean) plasma concentration ratio for M3G/M6G of  $5.0 \pm 0.3$  was comparable with the value of  $5.5 \pm 0.9$  reported by Osborne *et al.* (1990) after an intravenous dose of morphine given to healthy volunteers and  $6.4 \pm 0.5$  determined in cancer patients given chronic oral doses of morphine (Somogyi *et al.*, unpublished observations). However, it was lower than the value of  $9.4 \pm 0.7$  ( $\pm$  s.e. mean) found by Säwe (1986) in cancer patients during chronic oral dosing with morphine. The latter author employed the h.p.l.c. method of Svensson *et al.* (1982) with u.v. detection and, without an authentic sample of M6G, assumed a similar molar absorptivity to that of M3G. With an authentic sample of M6G in the present study, it was found that M3G exhibited a 52% greater u.v. response than M6G (based on chromatographic peak areas), which may explain the higher value obtained by Säwe (1986) for the M3G/M6G ratio.

When morphine was given orally to patients with normal renal function, the mean ( $\pm$  s.d.) ratio of the area under the plasma concentration-time curve of M3G to that of morphine was  $24.3 \pm 11.4$  (range 11.2 to 42.9) while for M6G to morphine the ratio was  $2.7 \pm 1.4$  (range 1.0 to 6.1) (Säwe, 1986). However, when morphine was given orally to patients with renal failure, the plasma concentrations of M3G and M6G were markedly increased relative to morphine (Peterson *et al.*, 1990; Säwe, 1986). This suggests that the elimination of the glucuronides was decreased since the total clearance of morphine is not significantly impaired by renal dysfunction (Säwe & Odar-Cederlöf, 1987; Woolner *et al.*, 1986). Osborne *et al.* (1986) and Don *et al.* (1975) reported cases of morphine intoxication in patients with renal failure and Osborne *et al.* (1986), finding markedly elevated plasma concentrations of M3G and M6G in the

absence of measurable concentrations of morphine, attributed the effect to the accumulation of M6G. Regnard & Twycross (1984) found that pain in patients with impaired renal function was controlled with below average doses of morphine.

Earlier studies of the effect of renal function on the elimination of M3G and M6G have provided limited data. Säwe & Odar-Cederlöf (1987) observed an accumulation of both M3G and M6G and a significant correlation between the half-life of M3G and the plasma concentration of urea in patients with renal failure. Peterson *et al.* (1990) found that, with decreasing creatinine clearance (predicted from the Cockcroft-Gault formula) in patients dosed orally with morphine, the trough plasma concentration of either glucuronide increased relative to the trough plasma concentration of morphine. After intravenous administration of M6G to two patients, one with normal and the other with impaired renal function, Osborne *et al.* (1988) observed that the plasma clearance of M6G was similar to creatinine clearance. Wolff *et al.* (1988) have shown a significant correlation between the plasma clearance of total glucuronides (determined as morphine after hydrolysis of the glucuronide metabolites with  $\beta$ -glucuronidase) and the plasma clearance of EDTA. However, in doing so, the authors assumed that a constant fraction of the intravenous dose of morphine was metabolized to the glucuronides in all patients. In addition, by not measuring the individual glucuronides, it was impossible to assess the effect of varying renal function on the clearance of either compound. The results of the present study demonstrate a significant relationship between the renal clearance of morphine, M3G and M6G, and renal creatinine clearance.

Renal function in the clinical setting is usually assessed from the determination of plasma creatinine concentration. In the present study, an automated colorimetric method and a more specific h.p.l.c. method were used to determine plasma creatinine. While there was a significant relationship between the two methods, values obtained by the colorimetric procedure were approximately 14% greater than those determined by h.p.l.c. and may reflect the lack of specificity with the Jaffe method. However, plasma creatinine concentration, as such, is not a reliable indicator of renal function since it is dependent not only on renal creatinine clearance, but also on the rate of appearance of creatinine in plasma, the latter dependent on the muscle mass of the patient and on dietary protein intake. In the clinical setting and without a urine collection, it was found previously that a suitable indicator of renal function was renal creatinine clearance predicted from a nomogram which includes age, sex and body weight (Cockcroft & Gault, 1976). The clinical details of the patients studied by Cockcroft & Gault (1976) were not given, although those patients with a urinary creatinine output of less than  $10 \text{ mg kg}^{-1}$  per 24 h and with successive daily plasma creatinine concentrations differing by more than 20% were excluded. The nomogram developed by the above authors, however, may be inappropriate for severely ill patients in an intensive-care unit. In the present study, three of the patients showed evidence of decreasing renal function prior to the study and eight had a urinary creatinine output of less than  $10 \text{ mg kg}^{-1}$

per 24 h, findings common to severely ill patients. The regression between  $CL_{Cr,pred}$  and  $CL_{Cr,meas}$  in the present study, revealed a slope (0.686) and intercept (26.3) not significantly different ( $P > 0.4$ ) from the respective values of 0.81 and 14.0 reported by Cockcroft & Gault (1976). However, when studying a large group of intensive-care patients, Martin *et al.* (1990), using the Jaffe method, found no significant relationship between creatinine clearance predicted from the Cockcroft-Gault formula and measured creatinine clearance. It may be that a modified nomogram derived from a larger group of severely ill patients would be more appropriate. Nevertheless, in the absence of a more suitable nomogram and with an insufficient number of patients included in the present study to allow one to be formulated, the Cockcroft-Gault formula was chosen to predict creatinine clearance because of its previously demonstrated reliability in subjects with varying degrees of renal function (Luke *et al.*, 1990) and its widespread use.

Given that the major route of elimination of the glucuronide metabolites is by renal excretion, it would be expected that, for a given dose of morphine, as renal function decreases the plasma concentrations of both M3G and M6G would increase. Indeed, with decreasing  $CL_{Cr,pred}$ , there was an increase in the dose-normalised plasma concentrations of both glucuronides. Moreover, Spearman Rank analysis revealed a significant association between the dose-normalised plasma concentrations of M3G and M6G and the reciprocal of  $CL_{Cr,pred}$  (Figure 2). This may provide a means of predicting the plasma concentrations of M6G likely to be achieved during intravenous infusion with a given dose rate of morphine in intensive-care patients. However, in addition to the comments regarding the prediction of creatinine clearance in these patients from plasma creatinine, the above prediction concerning M6G should be tempered further; firstly by the difficulty in measuring body-weight accurately in patients who further deteriorate during a prolonged stay in the intensive-care unit and, secondly, by the probability that, in some of the patients included in the present study, steady-state plasma concentrations of M3G and M6G will almost certainly not have been fully achieved.

The mean fraction unbound in plasma for morphine of 0.74 is comparable with the value of 0.65 found by Olsen *et al.* (1975) and 0.80 by Patwardhan *et al.* (1981) for healthy volunteers. The fraction unbound was marginally greater (0.69) in patients with renal failure (Olsen *et al.*, 1975). It may be assumed, therefore, that in the present study the mean fraction unbound of 0.74 determined in healthy subjects would approximate that in the fourteen patients. Similar assumptions may be made for the in-

fluence of renal impairment on the plasma binding of M3G and M6G, both compounds having a lower plasma binding compared with morphine. The mean values for the fraction unbound of M3G and M6G in human plasma, 0.85 and 0.89, respectively, have not been previously reported.

Shemesh *et al.* (1985) and Rapoport & Husdan (1968) have shown that renal creatinine clearance is not a true measure of glomerular filtration rate (GFR). In both studies renal creatinine clearance overestimated GFR, notably at lower values of true GFR (inulin clearance), and was attributed to the increasing fractional contribution of creatinine tubular secretion to renal clearance. Nevertheless, for the type of patients included in this study, renal creatinine clearance remains the most convenient method for estimating renal function.

The unbound renal clearance of morphine was found to be significantly greater than GFR, suggesting net secretion of morphine into urine during passage through the kidney. The unbound renal clearances of M3G and M6G were not significantly different from GFR, suggesting negligible net secretion or reabsorption after filtration at the glomerulus. These conclusions were not altered if approximate corrections, from the data of Shemesh *et al.* (1985), were made to creatinine clearance values to achieve more realistic estimates of GFR.

The results of the present study are supported by the findings of Garrett & Jackson (1979) in the dog. These authors found that the unbound renal clearance of morphine was greater than GFR while the unbound renal clearance of M3G was similar to GFR. Studies in the chicken (Hakim & Fujimoto, 1971; May *et al.*, 1967) suggest that a cation transport system is responsible for the active secretion of morphine. Further studies are needed to elucidate the mechanisms by which M3G and M6G are excreted by the human kidney. This may be important in predicting the likely effects of concomitant drugs (or their metabolites) which may be excreted by similar mechanisms.

In conclusion, both the relationship between renal function and the renal clearances of M3G and M6G, and the predicted plasma concentrations of the glucuronides likely to be achieved in patients of diverse renal function may be useful clinically. However, a greater understanding of the pharmacodynamics of morphine, M3G and M6G in humans will be required before the findings of the present study can be fully utilised.

This work was supported by the Anti-Cancer Foundation of the Universities of South Australia, and the Royal Adelaide Hospital Research Fund. The authors wish to thank Cathy Danz for her clinical assistance.

## References

- Abbott, F. V. & Palmour, R. M. (1988). Morphine-6-glucuronide: analgesic effects and receptor binding profile in rats. *Life Sci.*, **43**, 1685-1695.
- Cockcroft, D. W. & Gault, M. H. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*, **16**, 31-41.
- Don, H. F., Dieppa, R. A. & Taylor, P. (1975). Narcotic analgesics in anuric patients. *Anesthesiology*, **42**, 745-747.
- Garrett, E. R. & Jackson, A. J. (1979). Pharmacokinetics of morphine and its surrogates III: morphine and morphine 3-monoglucuronide pharmacokinetics in the dog as a function of dose. *J. pharm. Sci.*, **68**, 753-771.
- Gong, Q.-L., Hedner, T., Hedner, J., Björkman, R. & Nordberg, G. (1991). Antinociceptive and ventilatory effects of the morphine metabolites: morphine-6-glucuronide and morphine-3-glucuronide. *Eur. J. Pharmacol.*, **193**, 47-56.
- Hakim, R. & Fujimoto, J. M. (1971). Inhibition of renal

- tubular transport of morphine by  $\beta$ -diethylaminoethyl-diphenylpropylacetate in the chicken. *Biochem. Pharmac.*, **20**, 2647–2662.
- Hasselström, J., Berg, U., Löfgren, A. & Säwe, J. (1989). Long lasting respiratory depression induced by morphine-6-glucuronide? *Br. J. clin. Pharmac.*, **27**, 515–518.
- Huang, Y.-C. & Chiou, W. L. (1983). Creatinine XII: Comparison of assays of low serum creatinine levels using high-performance liquid chromatography and two picrate methods. *J. pharm. Sci.*, **72**, 836–837.
- Luke, D. R., Halstenon, C. E., Opsahl, J. A. & Matzke, G. R. (1990). Validity of creatinine clearance estimates in the assessment of renal function. *Clin. Pharmac. Ther.*, **48**, 503–508.
- Martin, C., Alaya, M., Bras, J., Saux, P. & Gouin, F. (1990). Assessment of creatinine clearance in intensive care patients. *Crit. Care Med.*, **18**, 1224–1226.
- May, D. G., Fujimoto, J. M. & Inturrisi, C. E. (1967). The tubular transport and metabolism of morphine-N-methyl- $C^{14}$  by the chicken kidney. *J. Pharmac. exp. Ther.*, **157**, 626–635.
- Milne, R. W., Nation, R. L., Reynolds, G. D., Somogyi, A. A. & Van Crugten, J. T. (1991). High-performance liquid chromatographic determination of morphine and its 3- and 6-glucuronide metabolites: improvements to the method and application to stability studies. *J. Chromatogr.*, **565**, 457–464.
- Olsen, G. D., Bennett, W. M. & Porter, G. A. (1975). Morphine and phenytoin binding to plasma proteins in renal and hepatic failure. *Clin. Pharmac. Ther.*, **17**, 677–684.
- Osborne, R. J., Joel, S. P. & Slevin, M. L. (1986). Morphine intoxication in renal failure: the role of morphine-6-glucuronide. *Br. med. J.*, **292**, 1548–1549.
- Osborne, R., Joel, S., Trew, D. & Slevin, M. (1988). Analgesic activity of morphine-6-glucuronide. *Lancet*, **i**, 828.
- Osborne, R., Joel, S., Trew, D. & Slevin, M. (1990). Morphine and metabolite behaviour after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide. *Clin. Pharmac. Ther.*, **47**, 12–19.
- Patwardhan, R. V., Johnson, R. F., Hoyumpa, A., Sheehan, J. J., Desmond, P. V., Wilkinson, G. R., Branch, R. A. & Schenker, S. (1981). Normal metabolism of morphine in cirrhosis. *Gastroenterology*, **81**, 1006–1011.
- Pasternak, G. W., Bodnar, R. J., Clark, J. A. & Inturrisi, C. E. (1987). Morphine-6-glucuronide, a potent mu agonist. *Life Sci.*, **41**, 2845–2849.
- Paul, D., Standifer, K. M., Inturrisi, C. E. & Pasternak, G. W. (1989). Pharmacological characterization of morphine-6 $\beta$ -glucuronide, a very potent morphine metabolite. *J. Pharmac. exp. Ther.*, **251**, 477–483.
- Pelligrino, D. A., Riegler, F. X. & Albrecht, R. F. (1989). Ventilatory effects of fourth cerebroventricular infusions of morphine-6- or morphine-3-glucuronide in the awake dog. *Anesthesiology*, **71**, 936–940.
- Persson, M. P., Wiklund, L., Hartvig, P. & Paalzow, L. (1986). Potential pulmonary uptake and clearance of morphine in postoperative patients. *Eur. J. clin. Pharmac.*, **30**, 567–574.
- Peterson, G. M., Randall, C. T. C. & Paterson, J. (1990). Plasma levels of morphine and morphine glucuronides in the treatment of cancer pain: relationship to renal function and route of administration. *Eur. J. clin. Pharmac.*, **38**, 121–124.
- Rapoport, A. & Husdan, H. (1968). Endogenous creatinine clearance and serum creatinine in the clinical assessment of kidney function. *Can. med. Ass. J.*, **99**, 149–156.
- Regnard, C. F. B. & Twycross, R. G. (1984). Metabolism of narcotics. *Br. med. J.*, **288**, 860.
- Säwe, J. (1986). Morphine and its 3- and 6-glucuronides in plasma and urine during chronic oral administration in cancer patients. In *Advances in Pain Research and Therapy*, vol. 8, eds Foley, K. M. & Inturrisi, C. E., pp. 45–55. New York: Raven Press.
- Säwe, J. & Odar-Cederlöf, I. (1987). Kinetics of morphine in patients with renal failure. *Eur. J. clin. Pharmac.*, **32**, 377–382.
- Shemesh, O., Golbetz, H., Kriss, J. P. & Myers, B. D. (1985). Limits of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int.*, **28**, 830–838.
- Shimomura, K., Kamata, O., Ueki, S., Ida, S., Oguri, K., Yoshimura, H. & Tsukamoto, H. (1971). Analgesic effect of morphine glucuronides. *Tohoku J. exp. Med.*, **105**, 45–52.
- Smith, M. T., Watt, J. A. & Cramond, T. (1990). Morphine-3-glucuronide—a potent antagonist of morphine analgesia. *Life Sci.*, **47**, 579–585.
- Svensson, J.-O., Rane, A., Säwe, J. & Sjöqvist, F. (1982). Determination of morphine, morphine-3-glucuronide and (tentatively) morphine-6-glucuronide in plasma and urine using ion-pair high-performance liquid chromatography. *J. Chromatogr.*, **230**, 427–432.
- Tanguy, M., Malledant, Y., Le Verge, R., Gibassier, D. & Saint-Marc, C. (1987). Perfusion intraveineuse prolongée de morphine. Etude pharmacocinétique. *Ann. Fr. Anesth. réanim.*, **6**, 22–28.
- Watt, J. A., Cramond, T. & Smith, M. T. (1990). Morphine-6-glucuronide: analgesic effects antagonized by morphine-3-glucuronide. *Clin. exp. Pharmac. Physiol.*, **17**, Suppl., 83.
- Wolff, J., Bigler, D., Christensen, C. B., Rasmussen, S. N., Andersen, H. B. & Tønnesen, K. H. (1988). Influence of renal function on the elimination of morphine and morphine glucuronides. *Eur. J. clin. Pharmac.*, **34**, 353–357.
- Woolner, D. F., Winter, D., Frendin, T. J., Begg, E. J., Lynn, K. L. & Wright, G. J. (1986). Renal failure does not impair the metabolism of morphine. *Br. J. clin. Pharmac.*, **22**, 55–59.
- Yeh, S. Y., Gorodetzky, C. W. & Krebs, H. A. (1977). Isolation and identification of morphine 3- and 6-glucuronides, morphine 3,6-diglucuronide, morphine 3-ethereal sulfate, normorphine, and normorphine 6-glucuronide as morphine metabolites in humans. *J. pharm. Sci.*, **66**, 1288–1293.

(Received 29 October 1991,  
accepted 19 February 1992)