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Plasma and Cerebrospinal Fluid Concentrations of Morphine and Morphine Glucuronides after Oral Morphine

The Influence of Renal Failure

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Background: **In patients with renal failure, morphine may cause prolonged narcosis and respiratory depression. Accumulation of the pharmacologically active metabolite morphine-6-glucuronide (M-6G) may explain this effect of morphine in patients with renal failure. After a single oral dose, morphine and its conjugates were measured in the plasma and the cerebrospinal fluid (CSF) in patients with renal failure.**

Methods: **Eight patients with normal renal function and six patients with renal failure requiring dialysis were studied after operation under spinal anesthesia. Plasma and CSF concentrations of morphine, morphine-3-glucuronide (M-3G), and M-6G were measured by high-pressure liquid chromatography every 4 h for 24 h after an oral dose of 30 mg morphine.**

Results: **The area under morphine plasma concentration–time curve from 0 to 24 h increased from 38 ± 4 ng · ml^{-1} × h in patients with normal renal function to 110 ng · ml^{-1} × h in those with renal failure ($P < 0.01$). In patients with renal failure, plasma concentrations of M-3G and M-6G were higher at 4 h and remained at an increased level until the end of the study. The peak CSF concentration of morphine at 8 h was similar in those with renal failure or normal renal function, 1.8 ± 0.4 and 2.0 ± 0.6 ng · ml^{-1} respectively. M-3G and M-6G in CSF reached a maximum at 12 h in patients with normal renal function, whereas in those with renal failure the concentrations gradually increased so that the highest concentrations were observed at 24 h. At 24 h, CSF M-6G concentration was 15 times greater in patients with renal failure than in those with normal renal function.**

Conclusions: **We conclude that M-3G and M-6G readily cross the blood–brain barrier in patients with normal renal function or with renal failure. In patients with renal failure, the retention of plasma M-6G induces a progressive accumulation of this active metabolite in CSF; this accumulation may explain the increased susceptibility to morphine in patients with renal failure. (Key words: Analgesics, opioid: morphine. Kidney: renal failure. Pharmacokinetics: morphine. Pharmacology: morphine.)**

PROLONGED narcosis and ventilatory depression have been reported in patients suffering from renal failure treated with morphine.[1,2] Morphine is water-soluble and partly eliminated, unchanged in the urine,[3] and its pharmacokinetics are unaltered in patients with renal failure.[4,5] Compared with other central analgesics, morphine is less hydrophobic (as reflected by its low octanol–water partition coefficient)[6], resulting in its slow penetration into the brain[7] and its elimination, unchanged, in the urine.[3] Although renal failure does not influence the elimination kinetics of morphine in humans, its conjugated metabolites are retained in the plasma of patients with renal failure.[8–11] This, and the discovery that some morphine conjugates are active[12] and may contribute to the analgesic properties of morphine during chronic administration,[13,14] has raised the possibility that the increased susceptibility of patients with renal failure to morphine is due to retention of these active metabolites.[14] Since the analgesic effect of morphine-6-glucuronide (M-6G) was first described in the rat,[12] excess opioid effects, associated with high plasma concentrations of M-6G, have been reported in patients with renal failure.[8] Morphine glucuronides are highly polar metabolites unable to cross the blood–brain barrier. Therefore it is not certain that accumulation of morphine glucuronides in patients with renal failure increases transfer across the blood–brain barrier. However, M-6G and, to a lesser extent, morphine-3-

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glucuronide (M-3G), have been found to be far more lipophilic than predicted.[15] In this study, concentrations of morphine and its conjugates in plasma and cerebrospinal fluid (CSF) were measured in patients with normal renal function and in patients with renal failure, after a single oral dose of morphine.

Materials and Methods

Patients

The study was approved by the Ethical Committee on Human Research. With informed consent, eight patients with normal renal function (aged (± SEM) 67 ± 9 yr and weighing 71 ± 12 kg) and six patients receiving maintenance hemodialysis (aged 70 ± 2 yr and weighing 72 ± 13 kg) were studied. All patients underwent elective orthopedic or peripheral vascular surgery. None of the patients had received morphine for at least 2 weeks before surgery. All patients received continuous spinal anesthesia. An 18-G Tuohy needle was placed in the L3–L4 or L4–L5 interspace, and a 22-G polyethylene catheter inserted through the needle was left in place for 24 h. Bupivacaine 0.5% isobaric was given in repeated doses as necessary. A single 30-mg dose of morphine (controlled-release morphine sulfate) was given orally after the last dose of bupivacaine. If analgesia was required postoperatively paracetamol or buprenorphine were used.

Measurements

Serial samples of blood (5 ml into heparinized tubes) and of CSF (1 ml) were withdrawn before and every 4 h until 24 h after morphine administration. Blood samples were centrifuged immediately after sampling. The plasma and CSF samples were stored at −20°C until analysis. Plasma and CSF samples were assayed for morphine, M-3G, and M-6G.

Analysis of Morphine Glucuronides. Extraction of plasma and CSF samples was performed by the method of Venn and Michalkiewicz.[16] One milliliter of each sample was extracted and dried with a concentrator (SpeedVac, Savant Instruments, Bioblock Scientific, Paris, France). The dried eluates were then redissolved in a total volume of 250 μl liquid chromatography solvent. The extraction recoveries, 99 ± 2% for M-3G and 97 ± 3% for M-6G, were close those obtained by Venn and Michalkiewicz.[16] Concentrations of M-3G and M-6G were measured by reverse-phase liquid chromatography. The method was that of Venn and Michalkiewicz[16] with some modifications. Isocratic elution was conducted at 40°C at a constant flow of 1.3 ml/min^{-1} with a LiChoGraph system (Merck-Hitachi, Merck-Clevenot, Nogeut, France). The column used was a LiChroSpher 60 RP Select B (250 × 4 mm inner diameter, 5 μM particle size) with a precolumn (4 × 4 mm inner diameter) of the same phase (Merck-Clevenot). Solvent was 0.1% trifluoroacetic acid in 10% acetonitrile with 25 mM heptane 1-sulfonic acid. The fluorescence spectrophotometer was a dual monochromator (F1000, Merck-Hitachi). The excitation and emission wavelengths were 280 and 335 nm, respectively. Under these conditions, the retention times of M-3G, M-6G, morphine, and hydromorphone (internal standard) were 5.7, 8.1, 11.3, and 15.7 min respectively. The limit of detection of M-3G and M-6G was 1 $ng \cdot ml^{-1}$ when 1 ml plasma or CSF samples were extracted and 200 μl of extracted residue was injected (coefficient of variation < 20%). The intra- and interday reproducibilities of at least six replicate samples were 2.8% and 8.6% for M-3G and 4.5% and 9.7% for M-6G.

Analysis of Morphine. Morphine concentrations in samples were too low to be detected by the liquid chromatography method with adequate precision and reproducibility. Therefore a specific morphine radioimmunoassay was used.[4] The limit of detection of this method was 0.1 $ng \cdot ml^{-1}$ for morphine (coefficient of variation 1.5–16.4% in a range of 0.10–50 $ng \cdot ml^{-1}$). The cross-reactivity of morphine metabolites and endogenous opioid peptides was <0.2%. The intra- and interday reproducibilities were 2.9% and 2.5%, respectively. The area under the curve of plasma morphine concentration *versus* time from 0 to 24 h was measured by the trapezoidal method.

Statistical Analysis. Comparisons between patients with normal renal function and patients with renal failure were performed by the Mann-Whitney test. Differences yielding $P < 0.05$ were considered significant.

Results

The clinical characteristics of the patients are shown in table 1 and the biologic data in table 2. The patients did not differ with respect to age and body weight. The clinical course over the first 2 postoperative days was uneventful in both groups of patients. No overt signs of sedation or of respiratory depression were observed. Postoperative analgesic requirement was similar between the two groups of patients (table 3). In plasma and CSF samples, high-performance liquid chromatography performed on baseline samples revealed no peaks

Table 1. Clinical Characteristics of the Patients

Patient No.	Age (yr)	Weight (kg)	Treatment	Drugs*	Bupivacaine (mg)	Duration of Anesthesia (min)	Surgery
Patients with normal kidney function							
1	81	65	—	1, 2, 3	15	180	Total hip replacement
2	68	88	—	4, 5	15	220	Knee prothesis
3	75	63	—	6, 7, 8	12.5	150	Hip surgery
4	58	85	—	9	10	60	Iliofemoral bypass
5	69	57	—	5, 9	30	270	Femoral popliteal bypass
6	80	65	—	1, 2	15	150	Iliofemoral bypass
7	74	60	—	7, 8	15	150	Iliofemoral bypass
8	58	90	—	2, 7, 10	15	130	Iliofemoral bypass
Patients with renal failure							
1	67	63	HD	3, 4, 12, 13	17.5	160	Total hip prothesis
2	69	78	HD	8, 13, 14	32.5	190	Knee prothesis
3	79	81	HD	8, 11	20	105	Iliofemoral bypass
4	70	56	HD	2, 14	18	195	Hip prothesis
5	61	56	HD	12, 13	15	210	Hip prothesis
6	75	61	HD	5, 6, 7, 8	15	130	Hip surgery

HD = hemodialysis.

* 1 = prazozin; 2 = nicardipine; 3 = captopril; 4 = acebutolol; 5 = insulin; 6 = clonidine; 7 = nitroglycerin; 8 = diltiazem; 9 = nifedipine; 10 = propranolol; 11 = verapamil; 12 = erythropoietin; 13 = sodium polystyrene sulfonate; 14 = vitamin D subsitute.

that would interfere with measurements of morphine or its metabolites in normal renal function or renal failure. In patients with normal renal function, the maximum plasma concentration of morphine was observed at 4 h and then, the concentration progressively decreased (table 4). There were large interindividual variations in the plasma concentration of morphine in the two groups. The mean plasma concentration of morphine was significantly greater in patients with renal failure than in those with normal renal function at 20 and 24 h. The area under the morphine curve of plasma concentration *versus* time from 0 to 24 h was

Table 2. Biochemical Data

	Patient No.	Hematocrit (%)	Plasma Creatinine (μM)	Plasma Proteins (g/L)	Plasma K^+ (mM)	Plasma CO_3H^- (mM)
Patients with normal kidney function	1	36	106	66	3.8	28
	2	36	106	70	4.2	26
	3	39	87	69	3.9	25
	4	39	104	60	4.7	26
	5	30	80	61	3.8	33
	6	36	106	70	3.8	28
	7	37	97	62	3.6	32
	8	30	62	56	3.8	29
Patients with renal failure	1	27	1,133	58	4.9	25
	2	33	574	69	3.9	24
	3	30	820	66	5.5	29
	4	24	522	58	5.3	30
	5	29	690	53	5.5	21
	6	34	506	58	5.1	20

Table 3. Postoperative Analgesics in Patients with Normal Renal Function and with Renal Failure during the First 24 h

Patient No.	0–4 h	4–8 h	8–12 h	12–16 h	16–20 h	20–24 h
Normal						
1		Paracet				
2					Paracet	Bupre
3	Paracet	Bupre				
4					Paracet	
5				Paracet		Paracet
6		Paracet				Paracet
7						Paracet
8						Paracet
Renal failure						
1					Paracet	
2				Paracet		
3			Paracet	Bupre		
4		Paracet		Paracet		
5		Paracet				
6			Paracet			

Paracet = 1 g intravenous proparacetamol; Bupre = 0.3 mg intravenous buprenorphine.

38 ± 4 ng · ml^{-1} × h in patients with normal renal function but significantly increased ($P < 0.01$) in those with renal failure to 110 ± 11 ng · ml^{-1} × h. In patients with normal renal function, the maximum plasma concentration of M-3G and M-6G was observed at 4 h and then declined progressively till the end of the study. In cases of renal failure, patients' plasma M-3G was significantly ($P < 0.01$) increased compared with that in subjects with normal renal function at all times during the study. The concentration of M-3G reached a plateau after 8 h. The plasma concentration of M-6G was also significantly ($P < 0.01$) increased in patients with renal failure in comparison with those having normal renal function. The concentration of M-6G in plasma remained almost at a plateau value between 8 and 24 h.

The CSF concentration of morphine and its metabolites are shown in table 5. The concentration of morphine in CSF was similar in normal renal function and patients with renal failure with a maximum concentration observed after 8 h in the two groups. M-3G and M-6G were detected in the CSF of all patients. In those with normal renal function, the mean concentration remained between 9 and 22 ng · ml^{-1} for M-3G and 2

Table 4. Plasma Concentration of Morphine, Morphine-6-Glucuronide (M-6-G), and Morphine-3-Glucuronide (M-3-G) after 30 mg Oral Morphine in Patients with Normal Renal Function and with Renal Failure

Time (h)	Morphine		M-6-G		M-3-G	
	Normal	RF	Normal	RF	Normal	RF
4	5.7 ± 2.3	14 ± 3.1	31 ± 10	139 ± 32*	126 ± 41	354 ± 78*
8	4.7 ± 1.3	8.6 ± 1.8	23 ± 5	206 ± 29*	102 ± 55	409 ± 54*
12	1.8 ± 0.6	3.5 ± 0.4	12 ± 4	214 ± 23*	55 ± 12	394 ± 39*
16	1.1 ± 0.4	3.2 ± 0.4	6 ± 2	199 ± 18*	31 ± 8	412 ± 77*
20	0.9 ± 0.3	3.3 ± 0.5*	8 ± 2	218 ± 36*	17 ± 4	380 ± 91*
24	0.7 ± 0.2	2.8 ± 0.4*	4 ± 1	208 ± 26*	12 ± 4	403 ± 92*

Data are mean ± SEM (ng/ml).

RF = renal failure.

* $P < 0.01$ *versus* normal.

Table 5. Lumbar Cerebrospinal Fluid Concentration of Morphine, Morphine-6-Glucuronide (M-6-G), and Morphine-3-Glucuronide (M-3-G) after 30 mg Oral Morphine in Patients with Normal Renal Function and with Renal Failure

Time (h)	Morphine		M-6-G		M-3-G	
	Normal	RF	Normal	RF	Normal	RF
4	1.2 ± 5.1	0.9 ± 0.3	2.2 ± 0.8	2.5 ± 0.5	12.8 ± 4.7	5.1 ± 2.3
8	2.0 ± 0.6	1.8 ± 0.4	3.8 ± 0.9	5.9 ± 1.2	20.4 ± 5.0	11.5 ± 2.0
12	1.4 ± 0.4	1.7 ± 0.3	4.1 ± 0.7	13.0 ± 2.3*	21.1 ± 3.9	24.4 ± 4.8
16	0.8 ± 0.3	1.4 ± 1.2	3.0 ± 0.5	17.2 ± 3.4*	16.5 ± 2.7	31.6 ± 3.7*
20	0.5 ± 0.1	1.3 ± 0.2	2.5 ± 0.4	24.1 ± 3.1*	14.0 ± 2.9	39.6 ± 2.7*
24	0.3 ± 0.1	1.0 ± 0.2	1.8 ± 0.3	25.0 ± 4.0*	9.4 ± 1.6	47.4 ± 8.0*

Data are mean ± SEM (ng/ml).

RF = renal failure.

* $P < 0.01$ *versus* normal.

and 4 $ng \cdot ml^{-1}$ for M-6G. In patients with renal failure a progressive increase in the concentration of M-3G and M-6G was observed. At 24 h, M-3G and M-6G continued to increase and reached their highest value. At 24 h, M-6G was about 15 times greater in the CSF of patients with renal failure than in those with normal renal function.

Discussion

Our data demonstrate that M-3G and M-6G, which are retained in the plasma in patients with renal failure after a single dose of morphine, take advantage of the first-pass effect to accumulate progressively in the CSF. We deliberately gave morphine orally to obtain greater M-3G and M-6G concentrations in plasma.[17] According to the availability of oral morphine, 30 mg orally is equivalent to 10 mg parenterally in terms of unchanged morphine, but by giving morphine orally we achieved higher concentrations of M-3G and M-6G.

Renal failure may affect morphine pharmacokinetics in several ways: oral absorption, rate of hepatic biotransformation, elimination of morphine and its metabolites, and diffusion across the blood–brain barrier. Although it is difficult to delineate the influence of these different factors in a single study, our results provide new information about morphine and morphine metabolite distribution in humans.

The sensitivity of the analysis permitted us to detect morphine and its metabolites in the CSF of patients with and without renal failure and demonstrates that M-3G and M-6G cross the blood–brain barrier in significant concentrations. Our results in patients with normal function are similar to those of Poulain *et al.*,[18] who measured the CSF concentration of morphine and M-6G in two patients after an oral dose of 20 mg morphine. Maximum concentrations were found between 4 and 8 h, of 2 and 4 $ng \cdot ml^{-1}$ for morphine and 6 and 20 $ng \cdot ml^{-1}$ for M-6G.[18] The principal finding of the current study is the progressive increase in the concentration of M-3G and of M-6G in the CSF of patients with renal failure. Between 8 and 24 h after morphine administration plasma M-3G and M-6G remained constant in patients with renal failure. During this time however, CSF concentrations of M-3G and M-6G gradually increased. This demonstrates that the plateau plasma concentration of M-3G and M-6G caused an increase in transfer across the blood–brain barrier and that this transfer is progressive and was still rising after 24 h. Although our study did not focus about the clinical consequences of morphine accumulation we did not observe clinical evidence of respiratory depression or of abnormal sedation in patients with renal failure. In addition, the dose of analgesics required during the postoperative course were similar in the two groups.

The kinetics of oral morphine have been studied in patients treated for cancer and in surgical patients. In the latter studies, oral morphine was used as premedication or for titration of postoperative pain relief.[19] Although, the time of blood sampling did not allow us to determine the peak plasma concentration, the value of 5.7 $ng \cdot ml^{-1}$ observed after 4 h, is comparable to that of 6.0 $ng \cdot ml^{-1}$ observed by Manara *et al.*[19] in surgical patients receiving the same oral dose of morphine. In studies among cancer patients, peak plasma concentration of morphine are higher after the same dose of oral morphine[20] probably because absorption of mor-

phine may be higher in patients treated for chronic pain than in surgical patients. In surgical patients, absorption may be diminished during the postoperative course. The concentration of M-3G and M-6G we have found in patients with normal renal function are similar to those of previous studies.[19,20] The concentration of M-3G was about five times that of M-6G, and this ratio is similar to that reported after single doses[20] or repeated doses of oral morphine.[13]

In patients with renal failure, we observed a transient increase in the plasma concentration of morphine, and a more dramatic increase in that of M-3G and M-6G. The increased area under the curve of unchanged plasma morphine concentration *versus* time may be explained by increased absorption, delayed elimination or enterohepatic recirculation. No data are available to support the hypothesis that morphine or other related compounds may be absorbed in larger amount in patients with renal failure. Because elimination of unchanged morphine in urine accounts for only 10% of the dose in the first 24 h,[3] absence of renal function and renal elimination of unchanged morphine cannot explain an increased plasma concentration of morphine. Therefore, increased enterohepatic recirculation of morphine is a likely explanation in patients with renal failure.[21] In a previous study, we observed that the pharmacokinetics of morphine were unchanged when it was administered intravenously.[4] Renal failure may increase the availability of oral morphine in contrast to intravenous morphine, because enterohepatic recirculation will be enhanced by the retention of metabolites.[22] Renal failure causes a dramatic increase in the plasma concentration of metabolites. This has been observed after intravenous morphine by Chauvin *et al.*[4] and by Sear *et al.*[5] Morphine metabolites remained at a plateau between 12 and 36 h after an intravenous dose of 10 mg in patients without renal function whereas metabolites were undetected in controls at 24 and 36 h.[4] In patients undergoing kidney transplantation, two- and threefold increases in the maximum plasma concentration of M-6G and M-3G, respectively, in comparison with normal patients were found.[5] In the current study the increased plasma concentration of M-3G and M-6G was much more pronounced in patients with renal failure. In comparison with controls, M-3G increased by 200% in patients with renal failure and this result compares well with that of other studies,[9,10] the increase in M-3G being more pronounced when morphine was administered orally than parenterally.[10] We observed a more pronounced increase in M-6G in patients with renal failure. There are several studies demonstrating an important increase in M-6G in patients with renal failure.[4,8–10] Säwe and Odar-Cederlöf[9] could detect M-6G in only one patient with renal failure. In other patients interfering peaks did not allow accurate measurement of plasma M-6G in patients with renal failure.[9] Interfering peaks are a frequent finding in patients with renal failure because of retention of foreign compounds or metabolites; in our study, however, the method of detection was sensitive and specific enough to allow the detection of M-6G in all patients. In addition, no peak that may have interfered with the measurement of morphine and its metabolites was detected in plasma and CSF sampled before morphine was given. Osborne *et al*[8] also simultaneously measured plasma M-3G and M-6G in three patients with acute renal failure who had received large doses of morphine in intensive care units. In those patients, M-3G and M-6G concentrations were markedly increased several days after morphine was discontinued.[8]

We conclude that the retention of M-6G in the plasma caused by renal failure is associated to a progressive accumulation of M-6G in the CSF.

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