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Morphine Pharmacokinetics in Renal Failure

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The effect of chronic renal failure (RF) on the pharmacokinetics of morphine was studied in nine patients with end-stage RF, aged 58 ± 8 yr (SD), and in seven control patients, aged 58 ± 15 yr, undergoing peripheral surgery under general anesthesia. All patients received 0.2 mg·kg^{-1} as an intravenous bolus injection. Blood samples were collected over a 36 h period, and plasma concentrations were measured using a specific radioimmunoassay method. Unchanged morphine could be identified for only 12 h in all patients. The mean plasma concentrations of unchanged morphine were similar in the two groups, except in the first sample (5 min) where it was higher ($P < 0.05$) in RF group. Patients with RF had a significantly smaller ($P < 0.05$) central compartment (0.3 ± 0.2 l·kg^{-1} *versus* 0.8 ± 0.4 l·kg^{-1}) than in the controls. Volume of distribution at steady state was also significantly ($P < 0.05$) decreased in RF patients (2.8 ± 1.0 l·kg^{-1}) *versus* 3.7 ± 1.2 l·kg^{-1} in the normal patients. The total apparent volume of distribution, the elimination half-life, and the plasma clearance were similar in the two groups. Identical peak levels of morphine metabolites were observed in the two groups, but plasma concentration of morphine metabolites was undetectable after 12 h in the control group and remained at a high level of 82 ± 49 ng·ml^{-1} at 24 h and 83 ± 57 ng·ml^{-1} at 36 h in RF patients. In conclusion, RF did not alter elimination of unchanged morphine, but induced an accumulation of morphine metabolites over 36 h at least, a fact which could explain the prolonged effect of the drug observed in patients with RF. (Key words: Anesthetics, Intravenous: morphine. Kidney: renal failure. Pharmacokinetics: morphine.)

PROLONGED NARCOSIS AND VENTILATORY DEPRESSION due to morphine have been observed in patients suffering from chronic renal failure (RF).[1,2] It has been suggested that the prolonged effect of morphine in RF reflects delayed elimination of morphine or its breakdown products.[1,2] Although morphine is almost completely metabolized in the liver, there are two pharmacokinetic hypotheses to explain the increased response of morphine in RF. Glucuronidation of morphine by hepatic glucuronyl transferase is the principal route of its biotransformation. In humans, 85% of the administered dose is eliminated as morphine glucuronide metabolites, and only 10% as normorphine in urine.[3] Thus, the renal elimination of morphine glucuronides may be impaired in RF, resulting in the accumulation of conjugates. Enteric deconjugation followed by reabsorption of the parent drug and/or systemic deconjugation of morphine glucuronide is a possible mechanism of morphine accumulation in RF. This metabolic cycle has been observed in RF with drugs which are eliminated almost exclusively as glucuronides, such as oxazepam[4] and clofibrate.[5] Another alternative to morphine deconjugation is that morphine glucuronide itself may penetrate the central nervous system slowly and accumulates therein when the plasma levels of the morphine conjugates are sustained.[6]

In the present study, the pharmacokinetics of morphine were studied in normal patients and in patients with RF, using two radioimmunoassay techniques measuring either unchanged morphine or morphine metabolites.

Methods

Nine patients with chronic renal failure (RF), aged 58 ± 8 yr (mean ± SD) and weighing 72 ± 10 kg, and seven patients with normal renal function (NL), aged 58 ± 15 yr and weighing 63 ± 8 kg, took part in the study after giving their informed consent. The study was approved by the Institutional Board of Paris 5 University. Four patients had been dialyzed within 24 h prior to surgery, and five patients had not yet required dialysis, but had creatinine clearances below 10 ml·min^{-1}. All patients had normal hepatic function. NL patients were ASA P.S. I or II and scheduled for peripheral surgery. RF patients were scheduled for arterio-venous fistula. Premedication consisted of 2 mg lorazepam given orally 2 h before anesthesia. Anesthesia was induced with thiopental 5–8 mg·kg^{-1} IV. Vecuronium 80 μg·kg^{-1} was used to facilitate tracheal intubation. Anesthesia was maintained with 60% nitrous oxide in oxygen delivered by mechanical ventilation. Ventilation was adjusted to maintain end-tidal CO_2 approximately at 5% (Datascope® 500 CO_2 analyser). Nasopharyngeal temperature was monitored and maintained between 36.0° and 37.0° by surface warming. The duration of operation was 168 ± 30 min in RF and 162 ± 84 min in NL patients.

Five to ten minutes after induction of anesthesia, morphine hydrochloride, 0.2 mg·kg^{-1}, was given by an IV bolus (10 s) injection. In some cases, when the level of analgesia was insufficient, fentanyl was administered in repeated doses of 0.1 mg. Venous blood samples (5–10

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ml) were withdrawn into heparinized tubes from the arm opposite the site of injection just before, 5, 10, 15, and 30 min, and 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, and 36 h after the administration of morphine. Blood samples were centrifuged and plasma samples were stored at −20° C until analysis. Total morphine (morphine and its metabolites) was evaluated by radioimmunoassay using a ^{125}I-labelled morphine (Kit Abuscreen®, Roche Diagnostics, Hoffman-La Roche, Inc., Nutley, N. J.). The procedure was performed according to the manufacturer's instructions. The lowest concentration which could be reliably determined was 1 ng · ml^{-1}. This radioimmunoassay measures morphine as well as some metabolites of morphine, including, in humans, morphine glucuronides and normorphine.[7] Unchanged morphine was measured by a specific radioimmunoassay, which was developed in our laboratory. Morphine antiserum was raised in a goat by immunization with the N-carboxymethyl-normorphine conjugated to bovine serum albumin. The immunogen was prepared exactly as described by Gintzler et al.[8] Coupling morphine to carrier protein through the piperidine ring nitrogen provides conjugates which elicit antiserum that recognizes structural changes at the 3- and 6- position of morphine; cross reactivity to morphine 3-glucuronide, codeine, and 6-substituted analogs are less than 0.2%. The radioimmunoassay did not cross-react with other central analgesics, such as fentanyl, which were administered to some patients. The limit of detection of morphine was 0.1 ng · ml^{-1} with an appropriate mixing of antiserum and labelled morphine (^{3}H-morphine: 24 Ci · mmol^{-1}, Amersham SA, Les Ulis, France) at 40% binding capacity for the tracer. For these two radioimmunoassays, the coefficient of variation for inter- and intra-assays of reproducibility ranged from 5–10%. Morphine metabolites were calculated as follows: total morphine − unchanged morphine.[9] To evaluate the specificity of the radioimmunoassay, plasma morphine concentrations were also measured in some plasma samples from both groups using high-pressure liquid chromatography (HPLC), coupled with amperometric detection.[10] The coefficient of variation of the assay was less than 5%, and the lower limit of sensitivity of the assay was approximately 5 ng · ml^{-1} when 1 ml of plasma was assayed.

The plasma concentration (C) *versus* time data for morphine were fitted to either a two-compartment or a three-compartment pharmacokinetic model, using a non-linear least-squares regression program, IGPHARM.[11] A weighting function of $1/C^2$ was found to provide the best fit of the data. Choice of an appropriate model was determined by use of an F-test.[12] The following pharmacokinetic parameters were derived: elimination half-life ($t_{1/2}\beta$); volume of the central compartment (V_1); total apparent volume of distribution at steady state (Vdss); and plasma clearance (CL). The total apparent volume of distribution measured by the area method (Vdarea) as determined by the trapezoidal rule was also obtained. Mean values of these variables for each group of patients were compared using the two-tailed nonparametric Mann-Whitney U-test. Linear regression analysis was also performed to compare morphine concentrations measured by both radioimmunoassay and HPLC.

Results

The unchanged morphine plasma concentration decay curve was triexponential in 15 patients and biexponential in 1 patient in the RF group. In patients with RF, the plasma concentration of unchanged morphine averaged 325.2 ± 142.9 ng · ml^{-1} at 5 min after administration, and was significantly higher ($P < 0.05$) than that found in NL patients (193.8 ± 80.4 ng · ml^{-1}) (fig. 1). Thereafter, the decline of unchanged morphine in plasma was similar in both groups (fig. 1). The plasma concentrations of unchanged morphine were undetectable after 12 h in the two groups. The pharmacokinetic parameters are shown in table 1. V_1 and Vdss were decreased in the patients with RF, whereas Vdarea, $t_{1/2}\beta$ and CL were not significantly different between the two groups. Among RF patients, there was no significant difference in the pharmacokinetic parameters, whether the patients had been dialysed or not. The concentration of total morphine measured by the non-specific radioimmunoassay exceeded the concentration of unchanged morphine in all samples. Plasma concentration of morphine metabolites *versus* time plots after administration of morphine are also presented in figure 1. Identical peak levels of morphine metabolites were observed in the two groups, but the plasma concentration of morphine metabolites decreased after 2 h in the NL group and remained on a plateau throughout the time of the study in the RF group. Morphine metabolites were undetectable after 12 h in the NL group, but averaged 82 ± 49 ng · ml^{-1} at 24 h and 83 ± 57 ng · ml^{-1} at 36 h in the RF group.

Fifty plasma samples obtained from five NL patients and six RF patients were analyzed by both radioimmunoassay and by HPLC. There was a high degree of correlation between the plasma concentration measured by the two methods, when the plasma concentration was above 5 ng · ml^{-1} (RIA = 1.02 HPLC + 0.11, r = 0.996, $P < 0.01$) (fig. 2). The slope of the linear relationship was situated between 0.983 and 1.048, with a confidence limit of 99%.

Discussion

Unchanged morphine concentrations were not modified by RF, except at 5 min. This transient increase in the plasma concentration of morphine will have little in-

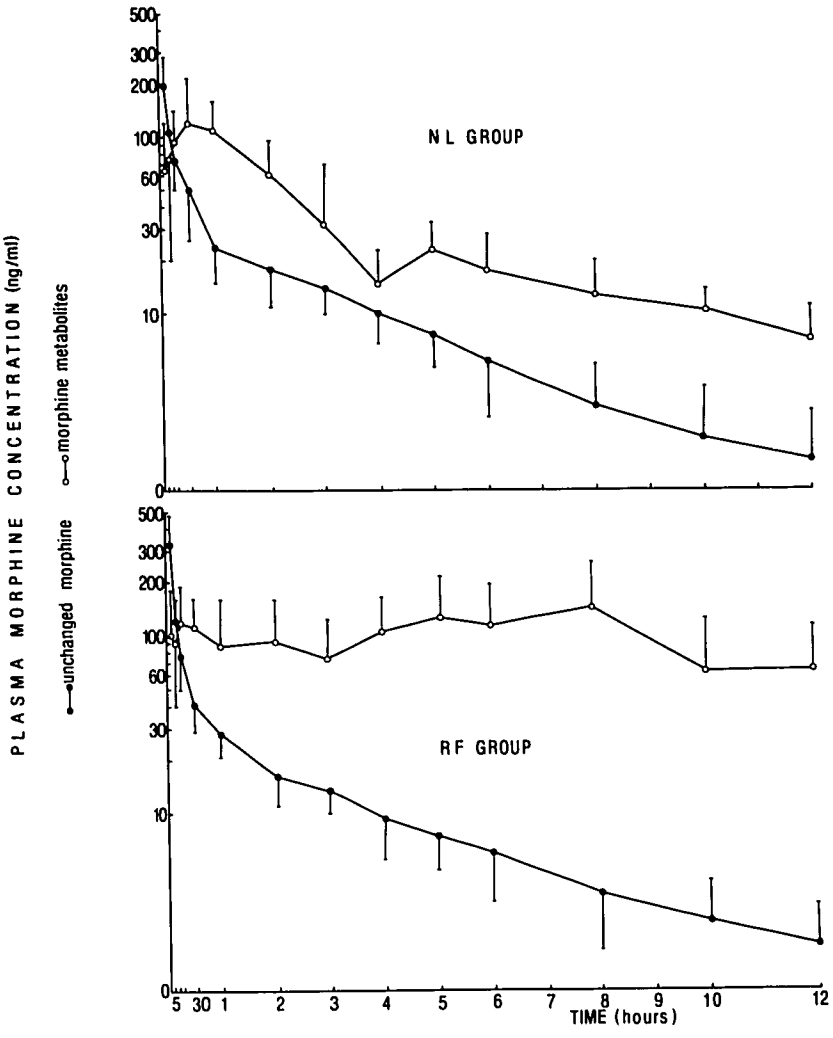

FIG. 1. Plasma levels (mean ± SD) of unchanged morphine (closed circles) and morphine metabolites (open circles) in normal (NL) and renal failure (RF) groups.

fluence on the penetration of morphine into the brain because of the slow uptake of morphine into cerebrospinal fluid, since the peak concentration of morphine in the cerebrospinal fluid occurs 15–30 min after IV injection.[6] The slow brain diffusion of morphine explains that its clinical effect reaches a maximum 30–60 min after IV administration.[6]

The average values for CL, Vdss, and $t_{1/2}\beta$ in the NL group were close to those reported by others using analytical methods specific to unchanged morphine, such as gas chromatography,[13] HPLC,[10] or radioimmunoassay.[9,14] The specificity of the radioimmunoassay used in the present study was confirmed by the similarity of the results between the radioimmunoassay and the HPLC. The mean CL in RF patients was 19% less than that in NL subjects, although this change was not significant. The absence of a significant decrease of morphine CL in RF suggests that renal elimination of unchanged morphine is negligible. In NL subjects, urinary elimination of unchanged morphine accounts for only 10% of the dose.[3] Aitkenhead *et*

TABLE 1. Effect of Renal Failure on the Pharmacokinetics of Unchanged Morphine.

Patient Group	V_1 ($l \cdot kg^{-1}$)	Vdarea ($l \cdot kg^{-1}$)	Vdss ($l \cdot kg^{-1}$)	$t_{1/2}\beta$ (min)	CL ($ml \cdot min \cdot^{-1} kg^{-1}$)
Normal	0.8 ± 0.4	5.4 ± 1.2	3.7 ± 1.2	186 ± 55	21.3 ± 6.3
Renal failure	0.3 ± 0.2*	4.6 ± 1.5	2.8 ± 1.0*	185 ± 53	17.1 ± 4.2

*$P < 0.05$.
V_1: initial volume of distribution; Vdarea: total apparent volume of distribution; Vdss: total apparent volume of distribution at steady state; $t_{1/2}\beta$: elimination half-life; CL: plasma clearance.

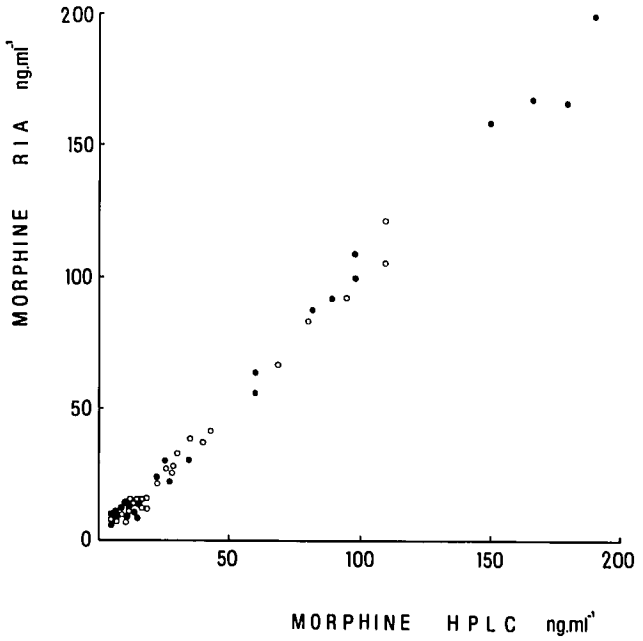

FIG. 2. Relationship between morphine plasma concentration measured by high pressure liquid chromatography (HPLC) and by radioimmunoassay (RIA) in normal (closed circles) and renal failure (open circles) patients ($y = 0.11 + 1.02x$, $r = 0.996$, $P < 0.01$).

al.[15] also showed morphine CL to be unmodified in patients with RF. This pharmacokinetic study was undertaken using a specific method of assay for morphine, HPLC, but was not followed after 2 h because of the lack of sensitivity of this method. In another study using a radioimmunoassay method in patients receiving cadaver kidney transplant, Moore *et al.*[16] showed that morphine plasma concentration paralleled creatinine plasma concentration, suggesting that the main route of elimination of morphine was renal. However, in this study, the plasma concentration of morphine metabolites was not measured, and it is questionable whether or not the assay method was truly specific for unchanged morphine. The V_1 and Vdss were reduced in patients in RF, and this had already been observed in a previous study.[15] The main decrease was in V_1, and may, in part, be related to the reduction of total body water in RF.[15] According to the present results, the prolonged effect of morphine in RF cannot be explained by an accumulation of unchanged morphine, since $t_{1/2}\beta$ and Cl were not altered in RF.

After IV administration of morphine, the plasma concentration of morphine metabolites increased rapidly, exceeding that of unchanged morphine as soon as 15 min after morphine injection. This has already been reported in patients with normal kidney function.[9,14] We observed the same initial rise in morphine metabolites, both in the RF group and in the NL group. The Abuscreen® antibody cross-reacts with morphine glucuronide and other metabolites. Murphy and Hug[9] demonstrated that this radioimmunoassay measured 89% of morphine glucuronide compared to standard solutions of morphine. Since morphine glucuronide is the major metabolite of morphine in humans,[3] the difference between the total morphine and free morphine accounts mostly for the amount of morphine glucuronide, although this measurement is indirect. In NL subjects, morphine glucuronide is readily excreted by the kidney, with the ensuing decrease in plasma concentration occurring within 4 h. In RF, morphine metabolites remained at a high level throughout the study. This accumulation did not cause a secondary increase in unchanged morphine concentration, suggesting that the mechanism of deconjugation of accumulating glucuronide, observed in RF for other drugs, such as oxazepam,[4] clofibrate,[5] or hydroxypropranolol,[17] does not exist for morphine. Therefore, a direct effect of the metabolites can be advanced as a mechanism of the prolonged effect of morphine in RF. Morphine glucuronides are active directly on the central nervous system, since intracerebral injections of morphine glucuronides produce analgesia and respiratory depression.[18,19] Morphine 3 glucuronide is a major metabolite of morphine,[20] which exhibits lower analgesic potency than morphine following intracerebroventricular administration in mice.[21] Morphine 6 glucuronide has been detected in small amounts from the urine of humans under normal circumstances, but it exhibits greater analgesic potency than does morphine,[22] and may be of considerable clinical importance if it accumulates in plasma. Morphine glucuronides are more polar- and less lipid-soluble than unchanged morphine, and this explains the slow rate diffusion of morphine metabolites into cerebro-spinal fluid observed in animals,[6] and the lack of effect of systemic morphine metabolites. In renal failure with the maintenance of high sustained plasma levels of metabolites, due to repeated administration of morphine, it is possible that morphine glucuronides could penetrate membranous barriers, such as those of the central nervous system, and induce prolonged respiratory depression.[6] Such a mechanism could explain the reported prolonged respiratory depression observed after the administration of the last dose of morphine in patients with renal failure.[1,2]

In conclusion, RF did not alter CL of morphine, but induced an accumulation of morphine metabolites at a high level over a long period. This may result in a prolonged effect of the drug after its administration in high or repeated doses.

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