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Renal failure does not impair the metabolism of morphine

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1 The pharmacokinetics of morphine were measured using gas chromatography-mass spectrometry (GCMS) with specific ion monitoring after the intramuscular administration of papaveretum to four patients with renal failure (one anephric) and three normals.
2 The apparent $t_{1/2}$ of absorption and $t_{1/2}$ of elimination were significantly shorter in the patients with renal failure ($P < 0.05$).
3 Morphine glucuronides are eliminated slowly in these patients as expected.
4 Renal failure does not impair the elimination of morphine.

Keywords morphine kidney failure gas chromatography pharmacology mass fragmentography

Introduction

Opioid drugs are widely used for premedication and for analgesia following surgery. Occasionally these drugs appear to have excessive effect in patients with renal failure (McQuay & Moore, 1984) in spite of the traditional belief that the liver is the main site of opioid metabolism. The results of recent studies using a 'specific' radioimmunoassay (RIA) for unconjugated morphine (Moore *et al.*, 1984a) have been interpreted as demonstrating an important role for the kidney in the metabolism of morphine. Moore *et al.* (1984b) reported on morphine disposition in 15 patients with end-stage renal failure during and after renal transplantation and showed that elimination did not occur until the transplant began to function. The same group (Ball *et al.*, 1985) demonstrated reduced morphine clearance in patients with renal dysfunction. The clearance of morphine was related linearly to creatinine clearance. Correspondence resulting from these papers has suggested that some people remain unconvinced about the specificity of the RIA method (Hanks & Aherne, 1985; Joel *et al.*, 1985; Säwe *et al.*, 1985) despite the reported good correlation with a high performance liquid chromatography (h.p.l.c.) method (Moore *et al.*, 1984a).

The aim of this study was to assess the elimination of morphine and morphine glucuronides in patients with renal failure after i.m. administration of papaveretum. Papaveretum i.m. (Omnopon®, Roche), is the most common opioid premedication used in our hospital, and contains between 47.5 and 52.5% anhydrous morphine (Martindale, 1982). Gas chromatography–mass spectrometry (GCMS) was selected as the analytical method to give the highest possible specificity.

Methods

The patients were four men, aged 34–60 years, on maintenance haemodialysis studied on a non-dialysis day. All patients were non-smokers, did not abuse alcohol and were taking iron and vitamin B supplements and aluminium hydroxide gel. One patient (7) was anephric. Each patient had a forearm fistula and normal liver function tests. The normal volunteers were three men, aged 34–41 years. The study was approved by the hospital ethics committee and all subjects gave informed consent. Papaveretum (0.25 mg kg^{-1} body weight) was injected into the deltoid

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muscle (fistula arm in the patients). Blood was obtained from a venous cannula in the contralateral arm immediately before injection and at intervals up to 24 h. Samples were collected into plain tubes and the serum separated and stored at −20° C until assayed.

The extraction procedure for morphine was based on previously reported methods (Ebbinghausen *et al.*, 1974; Yeh, 1975). All glassware was silanised before use. *N*-trideuteriomethylnormorphine ([$^2H_3$]-morphine) internal standard (Lee *et al.*, 1980) was added to the serum samples before extraction. For unchanged morphine, serum (1 ml) was mixed with acetone (6 ml), centrifuged for 5 min, the organic layer transferred to a clean 10 ml centrifuge tube and the acetone evaporated at 70–80° C under nitrogen. The dry residue was taken up in 0.01 M hydrochloric acid (1 ml) and washed with benzene (2 × 4 ml). The aqueous phase was adjusted to pH 8–9 by addition of 1 M sodium hydroxide, buffered to pH 8.9 with borate buffer (1 ml) and extracted twice with isopropyl alcohol-dichloroethane (3:10 v/v) on a vortex mixer. The combined organic phase was reduced in volume, transferred to a 1 ml Reacti-vial (Pierce Chemical Co, Rockford, Ill.) and evaporated to dryness at 70–80° C under nitrogen. The residue was reacted with bis(trimethylsilyl)acetamide or bis(trimethylsilyl)trifluoroacetamide (50 μl, both Pierce Chemical Co., Rockford, Ill.) in a sealed vial for 1 h at 60° C, and the resulting mixture used directly for GCMS analysis. Total morphine (conjugated and unchanged) was extracted and derivatised in the same way from serum previously incubated at pH 5 (0.2 M acetate buffer, 1 ml) with β-glucuronidase (Sigma G-0751, 2000 Fishman units) at 37° C for 24 h.

Analyses were performed on a Hewlett-Packard 5982A GCMS modified to permit the GC column to be inserted directly into the source block to within 1 cm of the ion chamber. The instrument was operated in chemical ionisation mode using ammonia reagent gas at *circa* 0.5 torr in the ion chamber, with a fused silica BP-1 capillary column (30 m × 0.32 mm i.d.; SGE Pty, Victoria 3134, Australia) and helium carrier gas at a flow rate of 3 ml min^{-1}. Injections (1 μl) were made at an oven temperature of 120° C using an OCI-3 on-column injector (SGE Pty); after the elution of volatiles the oven temperature was increased rapidly to 280° C, giving a retention time for bis(trimethylsilyl)morphine of about 8 min. At the completion of each run the oven temperature was held at 300° C for 5 min to remove higher boiling materials. Ions at m/z 433, 430 and 340 were monitored with a Hewlett-Packard 5947A multiple ion detector and the peak heights measured from the chart recorder. Standard weighed mixtures of morphine and [$^2H_3$]-morphine were added to plasma, extracted, derivatised and used as calibration standards.

The chemical ionisation mass spectrum of bis(trimethylsilyl)morphine with ammonia reagent gas gave an MH^+ ion at m/z 430 which was more intense than the only fragment ion at m/z 340. We therefore monitored MH^+ for morphine (m/z 430) and [$^2H_3$]-morphine (m/z 433) for quantitation, and used simultaneous detection of m/z 340 to rigorously establish morphine as the analyte. The average overall recovery of morphine from plasma at both 50 μg l^{-1} and 200 μg l^{-1} was about 80%. Accuracy was assessed by multiple determinations of a single standard plasma sample containing 30.0 μg l^{-1} morphine; measured levels were 29.3 ± 1.4 μg l^{-1} when [$^1H_3$]-morphine: [$^2H_3$]-morphine = 1. For peak height ratios out to about 240 min, all calibration lines (weighted linear least squares) had 8 or more points and correlation coefficients of better than 0.99; coefficients of variation for all points in this region were less than 11%. Beyond 240 min, the calibration line had r = 0.9815 and all points had c.v. < 16%. The use of plasma rather than serum for establishing calibration curves would not affect our conclusions.

Pharmacokinetic analysis

The concentration versus time data for each subject were fitted to a one-compartment open model with first-order absorption, using NONLIN (Metzler *et al.*, 1974). No advantage was gained by using a two-compartment model (*F*-ratio test). From the derived intercept and rate constants the area under the curve (AUC), time to peak (t_{max}), apparent absorption half-life ($t_{½}$ abs) and elimination half-life ($t_{½}$) were calculated conventionally. The clearance (CL) was calculated from

$$CL = \frac{FD}{AUC},$$

and the volume of distribution (V) from

$$V = \frac{CL}{k}$$

where F is the fractional bioavailability, assumed to be 1 (Stanski *et al.*, 1978), D is the dose (expressed as morphine sulphate equivalents) and k is the elimination rate constant. Pharmacokinetic parameters in normal and renal failure groups were compared using Student's unpaired *t*-test (two-tailed).

Table 1 Kinetic parameters of papaveretum disposition after intramuscular administration

Healthy volunteers	*Dose (mg)*	$t_{1/2}$ *abs (h)*	t_{max} *(h)*	$t_{1/2}$ *(h)*	*AUC* ($\mu g\, l^{-1}\, h$)	*CL* ($l\, h^{-1}\, kg^{-1}$)	V ($l\, kg^{-1}$)
1	13.3	0.13	0.56	2.13	161.2	1.03	3.17
2	15.3	0.11	0.51	2.42	130.7	1.30	4.54
3	13.3	0.03	0.21	1.97	112.0	1.52	4.33
Mean		0.09	0.43	2.17	134.6	1.28	4.01
± s.e. mean		0.03	0.11	0.13	14.3	0.14	0.43
Renal failure							
4	13.3	0.02	0.13	1.40	116.4	1.22	2.92
5	11.3	0.03	0.17	1.32	90.2	2.17	4.14
6	10.0	0.04	0.22	1.52	103.7	1.59	3.51
7	14.7	0.11	0.34	0.63	95.9	1.73	1.57
Mean		0.05	0.22	1.21	101.5	1.67	3.05
± s.e. mean		0.02	0.05	0.20	5.7	0.19	0.55
P value		0.03	0.10	0.02	0.1	0.19	0.24

Results (Table 1, Figures 1 and 2)

The apparent $t_{½}$ of absorption and the $t_{½}$ of elimination were significantly *shorter* in the patients with renal failure compared with the controls ($P < 0.05$) (Figure 1). The difference in mean CL and V corrected for body weight did not reach significance and so we cannot establish which component(s) is responsible for the decrease in the elimination $t_{½}$. The concentration time curve of morphine glucuronides, measured in two patients in renal failure, showed the expected plateau (Figure 2).

Discussion

Using GCMS we have been unable to confirm the observation (Moore *et al.*, 1984b; Ball *et al.*, 1985) that patients with renal failure have prolonged half-lives for morphine elimination. Indeed, our results suggest that patients with renal failure eliminate morphine more rapidly than normal subjects. It is worth noting that the anephric patient had the shortest half-life. The additional finding of a shorter apparent $t_{½}$ of absorption is not unexpected because cardiac output is greater in patients with renal failure

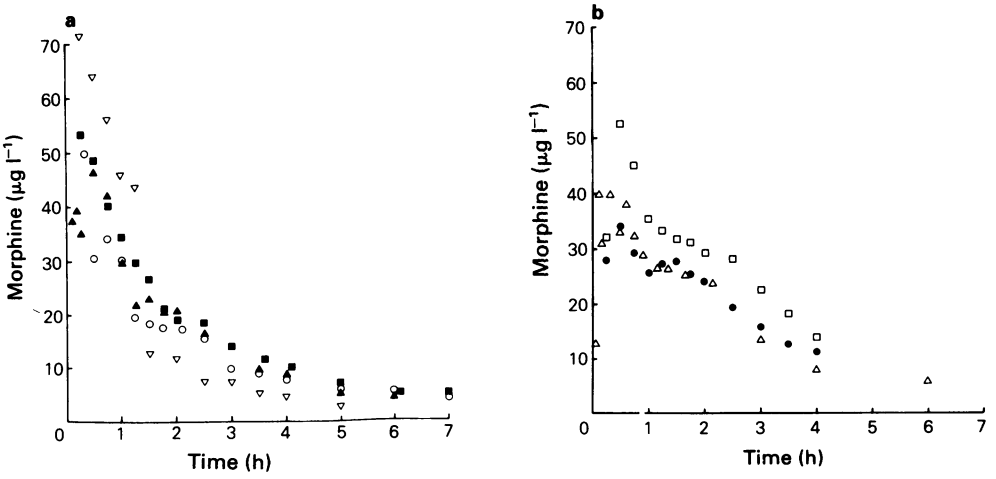

Figure 1 Plot of morphine concentrations after i.m. papaveretum (0.25 mg kg^{-1}) (a) four patients with renal failure (▽ anephric), (b) three healthy controls.

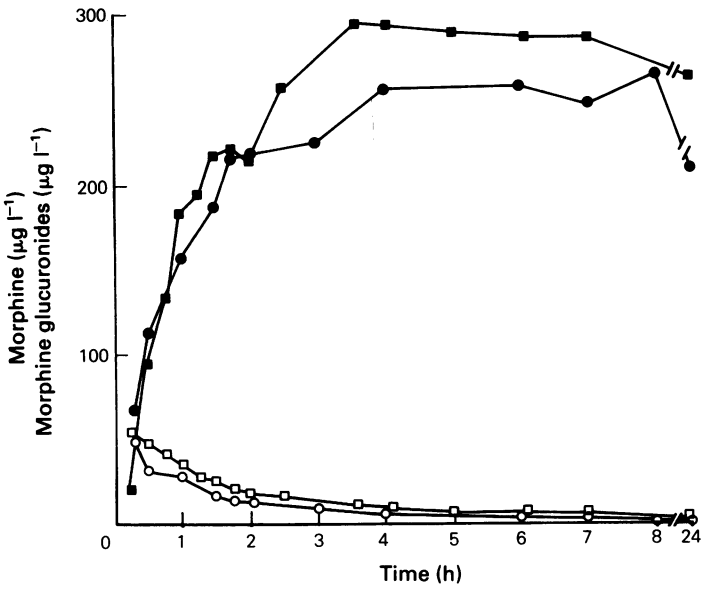

Figure 2 Plot of morphine (open symbols) and morphine glucuronides (closed symbols) concentrations for patients 4 and 5.

(Ikram *et al.*, 1983). Our results support those of Säwe *et al.* (1985) who used h.p.l.c. to measure morphine and its two glucuronides in seven patients with renal failure after intravenous administration of morphine. They found $t_{½}$ of elimination and clearance for morphine to be the same as for normal subjects.

Our serum extracts contained several compounds with GC retention times close to that of morphine. GCMS with specific ion detection is the only analytical method available which can unambiguously identify and quantitate morphine in such extracts. Any other separation method such as h.p.l.c. will have inherently lower resolution than capillary GC and is unlikely to be able to resolve all the co-extractants. Immunoassay methods do not rely on separation but require that co-extractants do not cross-react; the more of these present, and the less well-defined they are, the more difficult this is to establish. Our results suggest that immunoassay determinations of morphine in serum should be viewed with caution, especially in renal failure patients where the retention of water-soluble metabolites that are potentially immunologically cross-reactive is an additional concern (Joel *et al.*, 1985; Grabiuski *et al.*, 1983).

Our data do not explain the anecdotal observations made by many nephrologists of delayed recovery from the effects of opioids in patients with renal failure. However, in a prospective study (Woolner, unpublished data) patients on haemodialysis undergoing vascular access procedures and patients with normal renal function having other minor peripheral surgical procedures had similar recovery times after premedication with i.m. papaveretum. The results we have obtained using a highly specific analytical method, GCMS, show that renal failure does not impair the elimination of morphine.

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