

Bone density showed a significant decline with age in both races ( $p < 0.0001$ ). The mean age at menopause did not differ between the two groups (Polynesians 48.2 (SEM 0.9) years, Europeans 49.6 (0.5) years).

### Discussion

These data show that the bone mineral content of the distal forearm is higher in Polynesian women than in New Zealand women of European ancestry. This finding is consistent with the previously documented low incidence of femoral neck fractures in this group.<sup>2</sup>

The reasons for inter-racial differences in bone mass remain uncertain. While nutrition and lifestyle probably contribute in some instances, they are unlikely to be relevant to the present findings as both groups live in the same homogeneous society. In American blacks an increase in muscle mass has been shown<sup>3</sup> and has been suggested to be causally related to their higher bone density. The increased muscle mass, however, could also be regarded as an independent manifestation of a generalised increase in connective tissue mass. Recently differences in serum concentrations of parathyroid hormone and vitamin D metabolites have been found between American blacks and whites.<sup>4</sup> This may imply that race has

a major effect on the control of calcium metabolism or it may merely be a reflection of reduced cutaneous vitamin D synthesis secondary to dark skin colour. The former possibility is supported by the independent finding of higher calcitonin and katalcalcin levels in blacks.<sup>5</sup>

These findings indicate that high bone density is not unique to African races and that inter-racial differences in bone mass may be more common than was once thought.

We thank Mr Mike Province for his statistical help.

### References

- Christiansen C, Rodbro P, Jensen H. Bone mineral content in the forearm measured by photon absorptiometry. Principles and reliability. *Scand J Clin Lab Invest* 1975;35:323-30.
- Stott S, Gray DH. The incidence of femoral neck fractures in New Zealand. *N Z Med J* 1980;91:6-9.
- Cohn SH, Abesamis C, Yasumura S, Aloia JF, Zanzi I, Ellis KJ. Comparative skeletal mass and radial bone mineral content in black and white women. *Metabolism* 1977;26:171-8.
- Bell NH, Greene A, Epstein S, Oexmann MJ, Shaw S, Shary J. Evidence for alteration of the vitamin D-endocrine system in blacks. *J Clin Invest* 1985;76:470-3.
- Stevenson JC, Myers CH, Ajdukiewicz AB. Racial differences in calcitonin and katalcalcin. *Calcif Tissue Int* 1984;36:725-8.

(Accepted 11 March 1986)

## Morphine intoxication in renal failure: the role of morphine-6-glucuronide

RICHARD J OSBORNE, SIMON P JOEL, MAURICE L SLEVIN

### Abstract

Patients with impaired renal function may experience severe and prolonged respiratory depression when treated with morphine. This has been attributed to accumulation of the drug during renal failure. Three patients are described who had classical signs of intoxication with morphine in the absence of measurable quantities of morphine in the plasma. The observed clinical effect is attributed to accumulation of the pharmacologically active metabolite morphine-6-glucuronide, which is usually renally excreted. It is concluded that morphine does not accumulate in patients with renal failure but that accumulation of metabolites does occur.

The previously reported observations of morphine accumulation during renal failure probably result from the use of radio-immunoassays that cannot distinguish between morphine and morphine-6-glucuronide. Thus the apparent morphine concentration measured with these assays in fact reflects the total quantity of morphine and morphine-6-glucuronide present.

### Introduction

Patients with impaired renal function may experience severe and prolonged respiratory depression when treated with morphine. This sensitivity to morphine has been attributed to accumulation of the drug due to decreased metabolism or elimination.<sup>1</sup>

Imperial Cancer Research Fund, Department of Medical Oncology, St Bartholomew's Hospital and Homerton Hospital, London

RICHARD J OSBORNE, MRCP, Imperial Cancer Research Fund clinical research fellow

SIMON P JOEL, BSC, research assistant

MAURICE L SLEVIN, MD, MRCP, consultant physician

Correspondence to: Dr Richard J Osborne, ICRF Department of Medical Oncology, St Bartholomew's Hospital, London EC1A 7BE.

We report on the morphine and metabolite concentrations of three patients with renal failure who experienced pronounced respiratory depression apparently caused by treatment with morphine.

### Patients, methods, and results

**Case 1**—A 64 year old man with chronic renal failure (creatinine clearance 3 ml/min) underwent elective aortic aneurysm repair. Postoperatively he received 84 mg of Omnopon in 42 hours. (Omnopon comprises morphine and noscapine with small quantities of codeine and papaverine. Noscapine and papaverine have no analgesic or respiratory depressive effects.) Three days postoperatively, he developed respiratory depression, which necessitated mechanical ventilation, and treatment with Omnopon was stopped. No other respiratory depressant drugs had been given. Naloxone was given to maintain spontaneous ventilation, and 20.3 mg was required over the next eight days.

**Case 2**—A 39 year old woman with polycystic kidneys (plasma creatinine concentration  $>1000 \mu\text{mol/l}$  (11 mg/100 ml) required ventilation after a subarachnoid haemorrhage. She received 361 mg Omnopon over five days. Respiratory depression requiring ventilation and reversible by naloxone persisted for six days after treatment with Omnopon was stopped.

**Case 3**—A 70 year old man underwent emergency surgery for peritonitis and subsequently developed severe acute renal failure. He received 415 mg Omnopon over three days. Respiratory depression requiring ventilation persisted for three days after treatment with Omnopon was stopped.

During the long period of respiratory depression apparently induced by morphine in these patients plasma samples were collected and analysed using a high performance liquid chromatography assay.<sup>2</sup> This assay distinguishes and measures morphine and its major metabolites, morphine-3-glucuronide, morphine-6-glucuronide, and normorphine.<sup>3</sup> The table shows the concentrations of morphine, morphine-6-glucuronide, and morphine-3-glucuronide. (No normorphine was detected in any sample.)

### Discussion

We have described three patients with prolonged respiratory depression after treatment with morphine in the presence of

*Concentrations of morphine, morphine-6-glucuronide, and morphine-3-glucuronide in three patients with renal failure treated with Omnopon*

Time after treatment with Omnopon was stopped (h)	Respiratory depression	Morphine (nmol l <sup>-1</sup> )	Morphine-6-glucuronide* (nmol l <sup>-1</sup> )	Morphine-3-glucuronide† (nmol l <sup>-1</sup> )
<i>Case 1</i>				
153	Yes	<10	386	2040
165	Yes	<10	352	1930
198	Yes	<10	259	1210
390	No	<10	54	230
406	No	<10	60	<200
<i>Case 2</i>				
108	Yes	<10	848	3670
132	Yes	<10	701	2870
156	No	<10	468	2150
181	No	<10	279	1190
207	No	<10	141	730
<i>Case 3</i>				
40	Yes	39	2342	10220
62	Yes	<10	2026	9230
117	Yes‡	<10	1562	9720
135	Yes‡	<10	1350	7670
161	Yes‡	<10	1023	5040
185	Yes‡	<10	872	4940

\* Morphine-6-glucuronide elimination half life = 89 hours in case 1, 38 hours in case 2, and 103 hours in case 3.

† Morphine-3-glucuronide elimination half life = 75 hours in case 1, 41 hours in case 2, and 136 hours in case 3.

‡ Patient received fentanyl intermittently during this period.

Conversion: SI to traditional units—Morphine sulphate pentahydrate: 1 nmol l<sup>-1</sup> ≈ 0.38 ng ml. Morphine-6-glucuronide dihydrate: 1 nmol l<sup>-1</sup> ≈ 0.496 ng ml.

impaired renal function. Our results indicate that a state of narcotic intoxication may exist in the absence of measurable amounts of morphine in the plasma. This may be explained by the persistence in the plasma of large quantities of the metabolite morphine-6-glucuronide, which is usually excreted renally. Morphine-6-glucuronide (unlike morphine-3-glucuronide) is pharmacologically active in animals and, indeed, may be more potent than morphine itself.<sup>4</sup> We believe that our findings are the first recognised evidence of the pharmacological effect of morphine-6-glucuronide in man.

Previous studies of patients with renal failure seem to have shown abnormal elimination of morphine with reversion to normal when renal function returns after transplantation.<sup>1</sup> Extensive metabolism

of morphine in the kidney has been suggested as a cause of this phenomenon. These findings, however, have been based on a radioimmunoassay for morphine which has been found to cross react extensively with morphine-6-glucuronide.<sup>5</sup> Because more of this metabolite than morphine itself remains in the plasma after treatment with morphine, morphine concentrations measured with this radioimmunoassay in fact reflect the sum of morphine and morphine-6-glucuronide present, casting doubt on the results obtained with the assay.

The persistence of large amounts of morphine-6-glucuronide in the plasma, as described, is important for several reasons. Firstly, prolonged narcosis, long after the last dose of morphine is given, may result in incorrect diagnosis of cerebral damage in the obtunded patient. Secondly, respiratory depression lasting for many days exposes the patient to the complications of intubation and mechanical ventilation.

Finally, the fact that morphine-6-glucuronide may have been a confounding factor in many previous studies of morphine pharmacokinetics that used radioimmunoassay suggests that these studies should be re-evaluated, with greater emphasis placed on the role of morphine-6-glucuronide in the clinical effects of morphine.

We thank Dr C Hinds, Dr G Jeffries, Professor R Wood, and Dr L R I Baker of St Bartholomew's Hospital; Mr M G S Golby and Dr N Mathews, of Royal Devon and Exeter Hospital; and Dr C Thompson and Dr M S Neilson of Southampton General Hospital for their help and permission to report these cases.

## References

- Ball M, Moore RA, Fisher A, McQuay HJ, Allen MC, Sear J. Renal failure and the use of morphine in intensive care. *Lancet* 1985;ii:784-6.
- Svensson JO, Rane A, Sawe J, Sjoqvist F. Determination of morphine, morphine-3-glucuronide, and tentatively morphine-6-glucuronide in plasma and urine using ion pair high performance liquid chromatography. *J Chromatogr* 1982;230:427-32.
- Joel SP, Osborne RJ, Nixon NS, Slevin ML. Morphine-6-glucuronide—an important metabolite. *Lancet* 1985;ii:1099-100.
- Shimomura K, Kamata O, Ueki S, et al. Analgesic effect of morphine glucuronides. *Tohoku J Exp Med* 1971;105:45-52.
- Aherne GW, Littleton P. Morphine-6-glucuronide, an important factor in interpreting morphine radio-immunoassays. *Lancet* 1985;ii:210-1.

Accepted 14 April 1986.

# Treatment of cancer associated hypercalcaemia with combined aminohydroxypropylidene diphosphonate and calcitonin

S H RALSTON, A A ALZAID, M D GARDNER, I T BOYLE

## Abstract

Eight patients with cancer associated hypercalcaemia were treated with the combination of aminohydroxypropylidene diphosphonate and salmon calcitonin for six days. Serum calcium concentration fell significantly within 24 hours of starting treatment due to a reduction in bone resorption and renal tubular calcium reabsorption. In the longer term hypercalcaemia was controlled by a further progressive reduction in bone resorption, which persisted for six days after treatment was stopped. Renal tubular calcium reabsorption, however, remained suppressed

only during drug treatment. The rapid fall in serum calcium was attributable to the acute renal and skeletal effects of calcitonin, whereas in the longer term control of hypercalcaemia was due to diphosphonate mediated suppression of bone resorption.

In view of the rapid effect and lack of toxicity, combined treatment with aminohydroxypropylidene diphosphonate and calcitonin would be of particular value in patients with severe hypercalcaemia in whom a quick but sustained reduction in the serum calcium concentration is desired.

## Introduction

In a recent study aminohydroxypropylidene diphosphonate was found to give better long term control of hypercalcaemia of cancer than either mithramycin or corticosteroids plus calcitonin.<sup>1</sup> In the short term, however, aminohydroxypropylidene diphosphonate was the least effective agent because of its slow onset of action. We report the effects of combined treatment with aminohydroxypropylidene

University Departments of Medicine and Biochemistry, Glasgow Royal Infirmary, Glasgow G31 2ER

S H RALSTON, MRCP, senior registrar in medicine  
A A ALZAID, MB, BCH, senior house officer in medicine  
M D GARDNER, FRSC, principal biochemist  
I T BOYLE, FRCP, reader in medicine

Correspondence to: Dr Ralston.