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 ⁻¹)	Morphine-6-glucuronide* (nmol l ⁻¹)	Morphine-3-glucuronide† (nmol l ⁻¹)
Case 1				
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
Case 2				
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
Case 3				
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⁻¹ ≈ 0.38 ng ml. Morphine-6-glucuronide dihydrate: 1 nmol l⁻¹ ≈ 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.⁴ 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.¹ 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.⁵ 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.

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Treatment of cancer associated hypercalcaemia with combined aminohydroxypropylidene diphosphonate and calcitonin

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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.¹ 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 aminohydroxypropy-

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lidene diphosphonate and calcitonin in cancer associated hypercalcaemia.

Patients and methods

We studied eight patients with hypercalcaemia due to various malignant tumours. All were initially rehydrated with intravenous saline 3 litres daily for at least 48 hours, and drug treatment was then begun: aminohydroxypropylidene diphosphonate as an intravenous infusion of 15 mg daily and salmon calcitonin by subcutaneous injection 100 IU every eight hours. Both

Biochemical response to aminohydroxypropylidene diphosphonate and calcitonin. (Inset: Serum calcium concentrations *v* calcium excretion (Ca_E) (after Peacock *et al*).) Points are medians. Interrupted lines represent interquartile range. P=Time of presentation. Dotted lines indicate normal range.

* $p < 0.05$ and ** $p < 0.02$ from day 0 for serum calcium and for urinary calcium to creatinine ratio.

Conversion: SI to traditional units—Calcium: 1 mmol/l $\approx$ 4.0 mg/100 ml. Urine creatinine: 1 mmol $\approx$ 0.1 g.

agents were given for six consecutive days along with continued saline infusions of 2 litres daily to prevent dehydration. Biochemical measurements were made on fasting blood and urine samples using an autoanalyser (Technicon). Serum calcium estimation was adjusted for albumin concentration.¹ The paired Wilcoxon test was used for statistical analysis.

Results

Both serum calcium and the urinary calcium to creatinine ratio fell significantly and progressively between days 1 and 12 (figure). Urinary hydroxyproline to creatinine ratio also fell from a mean (SEM) of 63

(9.1) $\mu\text{mol}/\text{mmol}$ before treatment (normal $< 30 \mu\text{mol}/\text{mmol}$) to 38 (9.1) $\mu\text{mol}/\text{mmol}$ on day 1 and 42 (8.3) $\mu\text{mol}/\text{mmol}$ on day 12 ($p < 0.02$ and $p < 0.05$ respectively compared with pretreatment value). Serum creatinine concentration fell from 152 (22.5) $\mu\text{mol}/\text{l}$ (1.7 (0.3) mg/100 ml) at presentation (normal 40–130 $\mu\text{mol}/\text{l}$; 0.5–1.5 mg/100 ml) to 129 (20.9) $\mu\text{mol}/\text{l}$ (1.5 (0.2) mg/100 ml) after rehydration ($p < 0.05$). Creatinine fell further to 110 (19.6) $\mu\text{mol}/\text{l}$ (1.2 (0.2) mg/100 ml) on day 1 and 99 (20.5) $\mu\text{mol}/\text{l}$ (1.1 (0.2) mg/100 ml) on day 12 ($p < 0.02$ and $p < 0.05$ compared with pretreatment value).

In terms of the "normal" relation between the serum calcium concentration and excreted calcium per unit of glomerular filtrate (Ca_E) the calcium lowering effect of drug treatment was due to a further fall in renal tubular calcium reabsorption from that achieved by rehydration and to a reduction in filtered calcium load, as reflected by a downward and leftward shift of the serum calcium *v* Ca_E points between days 1 and 6 (figure, inset). The fall in filtered calcium load was in turn due mainly to reduced bone resorption (as reflected by the calcium to creatinine ratios) but partly to an improvement in glomerular filtration rate. After treatment was stopped (days 9, 12) the calcium *v* Ca_E points shifted vertically downwards, indicating that renal tubular calcium reabsorption had risen though bone resorption remained suppressed.

Discussion

In this study the rapid calcium lowering effect was largely due to an acute reduction in both bone resorption and renal tubular calcium reabsorption. A similar response was reported using the combination of corticosteroids and calcitonin¹ and was probably mediated by the renal and skeletal effects of calcitonin itself.² In accordance with previous findings, the reduction in renal tubular calcium reabsorption was sustained for the duration of treatment but not thereafter, and indeed in the longer term control of hypercalcaemia was achieved by suppression of bone resorption. This was almost certainly due to the more prolonged antiosteoclastic effect of the aminohydroxypropylidene diphosphonate.³ The small increase in urinary hydroxyproline to creatinine ratios which remained after treatment probably reflected release of hydroxyproline from non-skeletal tissues.¹ In all cases correction of hypercalcaemia was associated with an improvement in symptoms in the absence of any drug related side effects.

In this study the combination of aminohydroxypropylidene diphosphonate and calcitonin gave better long term control of hypercalcaemia than the corticosteroid and calcitonin regimen used previously and was more rapidly acting than aminohydroxypropylidene diphosphonate used alone.¹ Moreover, we encountered none of the serious side effects which limit the use of other drugs such as mithramycin and intravenous phosphate.⁴ Combined treatment with aminohydroxypropylidene diphosphonate and calcitonin may therefore be regarded as the treatment of choice in severe hypercalcaemia when a rapid but sustained effect is desired. As the main action of calcitonin was to "buy time" during the initial 48 hours while the diphosphonate took effect, it may be possible to limit use of calcitonin to this period with obvious advantages in terms of cost.

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