Relative importance of renal failure and increased bone resorption in the hypercalcaemia of myelomatosis

PJ HEYBURN,* JA CHILD,† AND M PEACOCK*

*From the *MRC Mineral Metabolism Unit, and the †Department of Haematology, The General Infirmary, Leeds LS1 3EX, UK*

SUMMARY In order to define the relative importance of renal failure and increased bone resorption in the hypercalcaemia of myelomatosis 22 untreated patients were studied, of whom 12 were hypercalcaemic. Most patients had malabsorption of radiocalcium from the gastrointestinal tract and evidence of increased bone resorption as assessed by fasting urinary hydroxyproline/creatinine ratio. The mean OHPr/Cr ratio, however, was similar in patients with and without hypercalcaemia. Renal failure and Bence Jones proteinuria occurred more frequently in the hypercalcaemic patients. In four patients with hypercalcaemia there was an increase in OHPr/Cr after saline infusion accompanied by an improvement in renal function and hypercalcaemia. Mithramycin given to the same patients further reduced hypercalcaemia, presumably by inhibiting bone resorption. It was concluded that the hypercalcaemia of myelomatosis is due to the combination of renal failure and increased bone resorption, but that the OHPr/Cr ratio in the untreated state is a poor indicator of the degree of bone resorption in hypercalcaemic patients.

A raised plasma calcium in patients with myelomatosis has been shown to affect prognosis adversely.¹ This hypercalcaemia is often attributed to excessive bone resorption, the production of which is poorly understood.

Renal failure, which is a more important prognostic factor, may be associated with and aggravated by hypercalcaemia, though renal insufficiency may be present long before there is an increase in plasma calcium.²

In order to clarify the relative importance of impaired renal function and increased bone resorption in the production of the raised plasma calcium, patients with myelomatosis have been studied and comparisons made between those with and without hypercalcaemia. We have also studied, in hypercalcaemic patients, the use of therapy aimed primarily at improving glomerular filtration rate, and compared this with the effects of mithramycin, which has been shown to reduce bone resorption in Paget's disease³ and hypercalcaemia in myelomatosis.⁴⁻⁶

Patients and methods

Twenty-two patients (10 females and 12 males) were

studied, all of whom fulfilled accepted clinical, haematological, biochemical, and immunological criteria for myelomatosis. Ten patients were normocalcaemic and 12 hypercalcaemic on initial investigation. All patients were studied after an overnight fast and were untreated in terms of cytotoxic therapy or glucocorticoids.

Fasting plasma calcium, phosphate, creatinine, and alkaline phosphatase and urinary calcium, phosphate, creatinine, and hydroxyproline were determined by methods previously reported, as were radiocalcium absorption, plasma 25-hydroxy vitamin D₃, and parathyroid hormone.⁷ Plasma calcium was corrected to allow for changes in plasma albumin and globulin by the method of Hodkinson.⁸ Values were corrected to a plasma albumin of 45 g/l and globulin 30 g/l.

Immunological investigations were carried out at the Supra Regional Protein Reference Laboratory, Putney Hospital. Paraproteins were detected by cellulose acetate membrane electrophoresis, typed by immunofixation⁹ and quantitated by scanning electrophoresis strips with Ponceau red dye.

Statistical methods used were the Student's *t* test and Fischer's test of exact probability.

Four hypercalcaemic patients were studied before and after infusion of normal (0.9%) saline, which

Accepted for publication 23 July 1980

Relative importance of renal failure and increased bone resorption in the hypercalcaemia of myelomatosis 55

was given at the rate of 6 litres in 24 hours. When a 'steady state' had been achieved (ie, both plasma calcium and renal function had ceased to improve after rehydration) the same four patients were given an infusion of mithramycin. The rate of infusion of intravenous saline was kept constant, and mithramycin, 25 µg/kg body weight per day diluted in 1 litre of normal saline, was administered over a period of 4 hours.

Results

The incidence of paraprotein types in our patients (Table 1) was similar to that reported in larger series.^{10 11} While there was no difference in the amount of circulating paraprotein between our normocalcaemic and hypercalcaemic patients, Bence Jones proteinuria was more common in those with a raised plasma calcium, and the paraprotein was less often

of IgG subclass. All patients whose total plasma calcium was raised were still hypercalcaemic when these values had been corrected for changes in albumin and globulin.

Both groups of patients had an increased urinary calcium (Table 2), although it was significantly greater in the hypercalcaemic patients. Renal tubular reabsorption of calcium was normal. Plasma phosphate was normal in both groups, but urinary phosphate was raised. Malabsorption of calcium occurred in both groups of patients but did not relate to the presence of renal failure or vitamin D deficiency. In the presence of malabsorption of calcium, the increased urinary calcium indicates increased bone resorption. Likewise, hydroxyproline excretion was raised in both groups but was not significantly different. Impaired renal function occurred more frequently in the hypercalcaemic group (7 of 12 patients, compared to only one patient in the

Table 1 Paraprotein abnormalities in this series

Paraprotein	Previous series	This series	Normocalcaemic	Hypercalcaemic	
IgG	53-55%	52%	76.9%	23.0%	P < 0.05
IgA	23-25%	28%	15.4%	41.7%	NS
IgD	0-1%	8%	7.7%	8.3%	NS
Bence-Jones	19-22%	12%	0	23.0%	NS
Urinary Bence-Jones protein		68%	46.2%	91.7%	P < 0.05
Mean serum paraprotein level			29.8 g/l	27.0 g/l	NS

P values refer to the differences between the normocalcaemic and hypercalcaemic patients.

Table 2 Fasting plasma and urine biochemistry in normocalcaemic and hypercalcaemic patients with myeloma

	Normal range	Normocalcaemic			Hypercalcaemic			P
		Mean	SEM	n	Mean	SEM	n	
Plasma calcium (mmol/l)	2.22-2.60	2.32	0.025	10	3.26	0.148	12	<0.001
Corrected plasma calcium (mmol/l)	2.22-2.60	2.33	0.026	10	3.29	0.146	12	<0.001
Urine Ca/Cr (molar)	<0.425	0.40	0.16	10	0.84	0.09	12	<0.025
Renal tubular reabsorption of calcium (mmol/l) GF	1.80-2.20	1.89	0.10	10	2.00	0.12	12	NS
Plasma phosphate (mmol/l)	0.80-1.45	1.13	0.043	10	1.27	0.085	12	NS
Urine P/Cr (molar)	<1.82	1.99	0.56	10	2.23	0.24	12	NS
Renal tubular reabsorption of phosphate (mmol/l) GF	0.70-1.40	1.14	0.13	10	0.87	0.09	12	NS
Plasma creatinine (µmol/l)	45-130	98.8	8.37	10	270.0	74.52	12	<0.05
Radiocalcium absorption (FR/h)	0.30-1.40	0.29	0.09	6	0.18	0.04	9	NS
Plasma 25 OH vitamin D ₃ (nmol/l)	>25.0	67.0	21.2	7	39.3	9.8	8	NS
Plasma parathyroid hormone (pg/ml)	125-375	232.3	60.7	6	244.0	100.2	10	NS
Plasma alkaline phosphatase (KA units)	3-13	16.2	6.13	9	10.3	1.01	12	NS
Urine OHP/Cr (molar)	<0.024	0.026	0.004	10	0.022	0.002	12	NS

Conversion: SI to traditional units

Plasma calcium 1 mmol/l ≈ 4 mg/100 ml

Ca/Cr 1 = 0.353

Tubular reabsorption of calcium 1 µmol/l GF ≈ 4 mg/100 ml GF

Plasma phosphate 1 mmol/l ≈ 3.1 mg/100 ml

P/Cr 1 = 0.274

Tubular reabsorption of phosphate 1 mmol/l GF ≈ 3.1 µg/100 ml GF

Plasma creatinine 1 µmol/l ≈ 0.0113 mg/100 ml

Plasma 25 OH vitamin D 1 nmol/l ≈ 0.4 ng/ml

OHP/Cr 1 = 1.16

normocalcaemic group). The mean plasma parathyroid hormone concentration was normal in both groups of patients, but three patients in the hypercalcaemic group and one who was normocalcaemic had increased values. Plasma alkaline phosphatase was similar in both groups and was in the high normal range in the majority of patients.

Saline infusion in four hypercalcaemic patients (Table 3) resulted in a fall in plasma calcium, a significant improvement in renal function, reduction in the renal tubular reabsorption of calcium, and an increase in calcium and hydroxyproline excretion. Mithramycin given to the same patients produced a further fall in plasma calcium within 14 hours of the infusion with a reduction in calcium and hydroxyproline excretion and no change in renal function and tubular reabsorption of calcium. The fall in urinary hydroxyproline excretion occurred within 4 hours of the start of mithramycin (Figure).

Discussion

This study confirms the suggestion that hypercalcaemia in myelomatosis is due to a combination of increased bone resorption and renal failure.¹² While initially there was no difference in the raised hydroxyproline excretions of the normocalcaemic and hypercalcaemic patients, there was a further rise in the OHPr/Cr ratio after saline infusion in four hypercalcaemic patients. We have not studied the prolonged use of saline infusions in these patients, but in another hypercalcaemic patient who had vitamin D intoxication a similar response to saline occurred and was sustained even when renal function had ceased to improve. In the presence of pre-renal failure the OHPr/Cr ratio does not appear to correlate with the degree of bone resorption, and

Changes in urine calcium and hydroxyproline excretion after mithramycin infusion in one hypercalcaemic patient.

Conversion: SI to traditional units

Ca/Cr 1 = 0.353

OHPr/Cr 1 = 1.16.

the increased hydroxyproline excretion after saline infusion is probably not due to increased excretion as a result of improved renal function but to abnormal renal handling of hydroxyproline. We have seen similar responses to saline infusion in other hypercalcaemias (unpublished observations). Urinary hydroxyproline, as a measurement of bone resorption in the presence of renal failure, should be used only after correction of salt and water depletion.

In our hypercalcaemic patients, eight were uraemic

Table 3 Changes in fasting plasma and urine biochemistry in four hypercalcaemic patients after 24 hours of saline infusion and 14 hours of mithramycin infusion

	Basal		Saline			Mithramycin		
	Mean	SE	Mean	SE	n	Mean	SE	n
Plasma calcium (mmol/l)	3.59	0.19	3.10	0.16	4	2.78	0.10	4+
Plasma creatinine (μ mol/l)	338.2	80.6	219.7	59.8	4*	210.5	53.2	4
Urinary Ca/Cr (molar)	0.99	0.17	1.61	0.33	4	0.97	1.12	4
Urinary OHPr/Cr (molar)	0.017	0.003	0.040	0.007	4	0.026	0.003	4
Renal tubular reabsorption of calcium (mmol/l) GF	2.02	0.19	1.64	0.13	4	1.63	0.13	4

* $P < 0.05$

* $P < 0.02$

Results obtained after saline infusion are compared to those obtained in the basal state, and the data after mithramycin administration are compared to those from the end of saline infusion.

Conversion: SI to traditional units

Plasma calcium 1 mmol/l $\approx$ 4 mg/100 ml

Plasma creatinine 1 μ mol/l $\approx$ 0.0113 mg/100 ml

Ca/Cr 1 = 0.353

OHPr/Cr 1 = 1.16

Tubular reabsorption of calcium 1 mmol/l GF $\approx$ 4 mg/100 ml GF

and hypercalcaemic on first presentation and had not previously been investigated. Two patients who had been screened previously developed hypercalcaemia and renal failure at the same time. Two were hypercalcaemic despite normal renal function. Progressive deterioration of renal function in patients with multiple myeloma is closely correlated with the presence of Bence Jones proteinuria,^{1 13} and this was confirmed in our study.

Most patients had malabsorption of radiocalcium, as has previously been reported using balance techniques.¹⁴⁻¹⁶ Calcium absorption is a function of plasma levels of the active vitamin D metabolite 1,25 dihydroxy vitamin D₃,¹⁷ which was not, however, measured in this study. While many signals affect 1,25 dihydroxy vitamin D synthesis, the major factors are parathyroid hormone, vitamin D status, renal function, and plasma calcium concentration. Both groups of patients in this study were nutritionally vitamin D replete, as assessed by plasma 25 hydroxy vitamin D levels, and parathyroid hormone concentrations were normal in all but four patients. Therefore, the two factors that could possibly have caused a decrease in 1,25 dihydroxy vitamin D₃ synthesis in the hypercalcaemic patients are the presence of hypercalcaemia and renal failure. The malabsorption of calcium in the patients with normal biochemistry is unexplained but may be due to the disease itself or a product of it. In two of the four patients with high plasma concentrations of parathyroid hormone, the high level could be explained by the presence of renal failure. In the other two patients, the increased concentrations may have been due to cross-reaction in the assay system by abnormal proteins.

While infusion of saline usually improves glomerular filtration rate and decreases hypercalcaemia, a normal plasma calcium is not always achieved. Mithramycin infusion in these patients produced a further decrease in plasma calcium by reducing bone resorption, as indicated by a fall in OHPr/Cr ratio. This confirms the results of Kiang *et al.*,¹⁸ who showed, using ⁸⁵Sr or ⁴⁵Ca kinetics, a reduction in bone resorption in patients with myelomatosis which occurred 6 to 12 hours after injection of mithramycin. Our data show a reduction in OHPr/Cr ratio within 4 hours of starting the infusion, and this early change suggests a direct action of the drug on bone resorption. In life-threatening hypercalcaemia, if there is an inadequate response to rehydration, it is reasonable to administer at least one infusion of mithramycin

unless there is marked thrombocytopenia, which may be aggravated.

References

- Alexanian R, Balcerzak S, Bonnet JD, Gehan EA, Haut A, Hewlett JS, Monto RW. Prognostic factors in multiple myeloma. *Cancer* 1975;**36**:1192-201.
- De Fronzo RA, Cooke CR, Wright JD, Humphrey RL. Renal function in patients with multiple myeloma. *Medicine* 1978;**57**:151-66.
- Condon JR, Reith SB, Nassim JR, Millard FJC, Hilb A, Stainthorpe EM. Treatment of Paget's disease of bone with mithramycin. *Br Med J* 1971;**i**:421-3.
- Godfrey TE. Mithramycin for hypercalcaemia of malignant disease. *Calif Med* 1971;**115**:1.
- Stamp TCB, Child JA, Walker PG. Treatment of osteolytic myelomatosis with mithramycin. *Lancet* 1975;**i**:719-22.
- Fillastre JP, Humbert G, Leroy J, Maitrot J, Deshayes P, Canonne MA. Furosemide, mithramycin and salmon calcitonin in hypercalcaemia. *Eur J Int Care Med* 1975;**1**:185.
- Nordin BEC. *Calcium, phosphate and magnesium metabolism*. Edinburgh, London and New York: Churchill Livingstone, 1976:469-89.
- Hodkinson HM. Serum calcium in a geriatric inpatient population. *Age Ageing* 1973;**2**:157-62.
- Kohn J, Riches PG. A cellulose acetate immunofixation technique. *J Immunol Meth* 1978;**20**:325-31.
- Hobbs JR. Paraproteins, benign or malignant? *Br Med J* 1967;**iii**:699-704.
- Osserman EF, Takatsuki K. Plasma cell myeloma: gamma globulin synthesis and structure. *Medicine* 1963;**42**:357-84.
- Nordin BEC. *Metabolic bone and stone disease*. Edinburgh and London: Churchill Livingstone, 1973:117-21.
- Garnick MB, Mayer RJ. Acute renal failure associated with neoplastic disease and its treatment. *Semin Oncol* 1978;**5**:155-65.
- Lazor MZ, Rosenberg L, Carbone P. Studies of calcium metabolism in multiple myeloma with ⁴⁵Ca and metabolic balance techniques. *J Clin Invest* 1963;**42**:1238-47.
- Bentzell CJ, Carbone PP, Rosenberg L. The effect of prednisone on calcium metabolism and ⁴⁷Ca kinetics in patients with multiple myeloma and hypercalcaemia. *J Clin Invest* 1964;**43**:2132-45.
- Skoog WA, Adams WS. Clinical and metabolic investigation of eight cases of multiple myeloma during prolonged cyclophosphamide administration. *Am J Med* 1966;**41**:76-95.
- Peacock M, Taylor GA, Brown WB. Measurement of plasma 1,25(OH)₂ vitamin D by protein binding assay and radioimmunoassay. In: Norman AW *et al.* eds *Vitamin D basic research and its clinical application*. Berlin, New York: Walter de Gruyter, 1979:179-82.
- Kiang DT, Loken MK, Kennedy BJ. Mechanism of the hypocalcaemic effect of mithramycin. *J Clin Endocr Metab* 1979;**48**:341-4.

Requests for reprints to: Dr PJ Heyburn, MRC Mineral Metabolism Unit, The General Infirmary, Great George Street, Leeds LS1 3EX.