PAPERS AND ORIGINALS

Treatment of Paget's Disease of Bone with Mithramycin

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Summary

We report data from three patients with severe Paget's disease of bone who were treated with mithramycin.

Mithramycin infusion resulted in a fall in plasma calcium, phosphate, alkaline phosphatase, and urinary hydroxyproline excretion. There was an improvement in calcium and phosphorus balance in two of the three subjects studied. A pronounced or complete relief of bone pain occurred in all three.

We suggest that mithramycin exerts its beneficial effect in Paget's disease of bone by stimulating parathyroid hormone release. The parathyroid hormone released has a predominantly anabolic action on bone since its catabolic action is blocked by mithramycin, which inhibits bone resorption.

Introduction

Though Paget's disease of bone may be asymptomatic and often limited to a small number of bones, there may be extensive skeletal involvement and severe bone pain. Treatment of the disorder with a high calcium and phosphate diet, vitamin D, parathyroidectomy, and fluoride have not proved uniformly satisfactory (Albright and Reifenstein, 1948; Albright and Henneman, 1955; Higgins *et al.*, 1955; Avioli and Berman, 1968). Calcitonin is at present being assessed in the treatment of Paget's disease of bone (Bijvoet *et al.*, 1968).

Mithramycin, an antibiotic derived from *Streptomyces plicatus*, has cytotoxic activities and has been used almost exclusively in the treatment of various tumours (Curreri and Ansfield, 1960; Parker *et al.*, 1960; Kofman and Eisenstein 1963). It inhibits RNA synthesis but not DNA synthesis (Goldberg, 1965; Yarbo *et al.*, 1966). Changes in calcium metabolism noted during mithramycin therapy (Jacobsen *et al.*, 1965; Parsons *et al.*, 1967) resulted in its administration to two patients with Paget's disease of the bone. Relief of bone pain and clear-cut effects on calcium and phosphorus metabolism occurred in these individuals (Ryan *et al.*, 1969).

We here report clinical and biochemical data on three patients with severe Paget's disease of bone who were treated with mithramycin.

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Patients and Methods

Clinical and biochemical details of the patients investigated are shown in the Table. Calcium and phosphorus balance studies were performed in all cases. Mithramycin 15μg/kg of body weight dissolved in 500 ml of 5% dextrose was administered daily by means of an intravenous infusion which lasted four to five hours. A five-day period of treatment with mithramycin alternated with a five-day period during which the drug was not given.

Balance study techniques and phosphate analysis have been reported (Walker and Collins, 1963). Faecal calcium and phosphorus values were corrected for barium sulphate, which was used as a continuous internal marker at a dose of 1 g/day. Faecal barium was measured by atomic absorption spectrophotometry (Unicam SP 90). Urinary inorganic phosphate was measured with the Technicon AutoAnalyzer method N4b. Calcium analysis was performed by atomic absorption spectrophotometry (Unicam SP 90), the method of Trudeau and Freier (1967) being used. Plasma alkaline phosphatase was measured with the Technicon AutoAnalyzer method Urinary hydroxyproline was measured by the method of Koevoet (1965).

Results

The calcium and phosphorus balance data, plasma calcium and phosphate levels, plasma alkaline phosphatase, and 24-hour urinary hydroxyproline values of the patients studied are given in the Table. During mithramycin infusion there

Clinical and Biochemical Details

Diet (mg/day)	Clinical Features	Drug	Days Treated	Plasma			Calcium Balance (mg/day)			Phosphorus Balance (mg/day)			Urine Hydroxyproline (mg/24 hr)
				Calcium (mg/100 ml.)	Phosphate (mg/100 ml.)	Alkaline Phosphatase (K.A. units)	Urine	Faeces	Balance	Urine	Faeces	Balance	
						Case 1							
Calcium 803 Phosphorus 1240	Bone pain	0	5	9·0	3·3	60	48	2060	−1305	696	1180	−636	294
		M	5	7·8	2·1	55	29	748	+26	870	568	−198	134
		0	5	9·3	3·3	49	23	710	+73	684	540	+16	208
		M	5	7·7	2·0	39	4	515	+284	900	460	−120	96
		0	5	9·4	3·2	37	1	371	+431	668	353	+19	188
		M	5	8·0	2·0	36	1	520	+282	854	485	−109	119
		0	5	8·7	2·2	31	1	444	+358	634	406	+200	163
		0	5	9·1	3·3	32	10	372	+421	662	405	+43	248
						Case 2							
Calcium 915 Phosphorus 1160	Headaches. Cardiac failure	0	5	8·4	3·3	86	52	1115	−246	563	860	−223	482
		M	5	7·8	3·8	87	38	736	+141	480	708	−28	296
		0	5	8·3	3·3	69	56	1085	−126	542	687	−69	468
		M	5	7·4	3·0	68	50	1178	−313	548	868	−256	268
		0	5	9·0	3·2	67	79	1248	−412	644	925	−409	410
		M	5	7·0	3·2	65	68	1140	−293	577	834	−251	276
		0	5	8·6	3·0	60	59	1160	304	549	798	−187	400
		0	20	8·4	—	37	—	—	—	—	—	—	—
						Case 3							
Calcium 749 Phosphorus 1160	Bone pain	0	5	9·2	3·8	75	368	695	−314	954	525	−319	368
		0	5	—	—	—	362	700	−313	928	544	−312	390
		0	5	9·1	3·8	100	310	746	−307	856	548	−240	379
		M	5	8·1	2·6	78	100	764	−115	820	568	−228	179
		0	5	9·5	4·0	76	302	718	−271	796	520	−156	336
		M	5	7·9	3·0	66	148	754	−153	896	546	−282	190
		0	5	9·4	3·7	52	336	634	−221	698	460	+2	390
		M	5	—	—	—	120	684	−55	896	445	−181	179
		0	5	9·3	4·2	50	310	556	−117	716	398	+46	319
		0	10	9·7	3·1	52	414	738	−453	884	482	−206	301

was a fall in plasma calcium in all cases and in plasma phosphate in Cases 1 and 3. Plasma calcium and phosphate rapidly returned to normal during the control periods.

The first five-day balance period in Case 1 is almost certainly incorrect and should be ignored. The other balance periods in Case 1, however, show a pronounced increase in calcium and phosphorus retention with a fall in faecal and urinary calcium. Plasma alkaline phosphatase and urinary hydroxyproline both fell. There was complete relief of bone pain after the second five-day infusion of mithramycin. Case 2 showed plasma calcium and alkaline phosphatase changes similar to Case 1. There was, however, no improvement in calcium and phosphorus balance, though there was a fall in plasma alkaline phosphatase and urinary hydroxyproline. This patient's plasma urea rose from 32 to 59 mg/100 ml during treatment with mithramycin but fell to 33 mg/100 ml over the next three months. Mithramycin infusion in Case 3 resulted in a fall of plasma calcium and phosphate. There was a decrease in urinary calcium with a noticeable improvement in calcium and phosphorus balance. Plasma alkaline phosphatase and urinary hydroxyproline fell and there was definite relief of bone pain.

Discussion

Our findings confirm that treatment with mithramycin relieves the pain of Paget's disease of bone. Bone pain has not recurred in any of our patients treated with mithramycin during a two to eight months follow-up period, and these findings are of significance in view of the relatively small dose (15 μg/kg/day) given. The only possible toxic effect of the drug encountered at this dosage was in Case 2, where a rise in plasma urea from 37 to 59 mg/100 ml occurred. This fell to 40 mg/100 ml while the patient continued treatment with mithramycin, and three months later had fallen to 33 mg/100 ml. The other side effects previously reported—namely, anorexia, nausea, vomiting, drowsiness, fever, thrombocytopenia, and hepatic damage—were not encountered with our lower dose regimen.

In Cases 1, 2, and 3 plasma calcium, alkaline phosphatase, and urinary hydroxyproline fell during mithramycin infusion. Plasma phosphate did not fall in Case 2 as in Cases 1 and 3, and there was increased phosphaturia in Cases 1 and 3 but not Case 2 during mithramycin infusion. The other interesting finding was that calcium balance improved in Cases 1 and 3 but not in Case 2.

The fall in plasma calcium noted during mithramycin infusion is probably related to decreased bone resorption. This concept is supported by the pronounced fall in urinary hydroxyproline excretion which mainly reflects bone resorption rates. Ryan *et al.* (1969) suggested that mithramycin has a cytotoxic action on overactive or excess numbers of osteoclasts. These workers also noted a prompt reduction in urinary hyroxyproline excretion and postulated a direct action of mithramycin on osteoclasts. It is possible that the slow fall in plasma alkaline phosphatase also reflects a decline in osteoblastic activity secondary to decreased bone resorption. The fall in plasma calcium noted during mithramycin infusion returned to normal levels fairly rapidly, suggesting increased parathyroid hormone release. This is supported by a fall in plasma phosphate and increased phosphaturia in Cases 1 and 3. In Case 2 the plasma calcium did not rise above 9 mg/100 ml and there was no fall in plasma phosphate or increased phosphaturia. The probable explanation of these findings was that parathyroid hormone production was less in Case 2 than in Cases 1 and 3. In Cases 1 and 3 there was a fall in urinary and faecal calcium, either during or immediately after the mithramycin infusion. It is known that parathyroid hormone increases intestinal and renal tubular reabsorption of calcium (Kleeman *et al.*, 1958; Bernstein *et al.*, 1963), so this may be the mechanism by which plasma calcium returns to normal values when bone resorption is inhibited by mithramycin.

The question arises whether the beneficial effect of mithramycin in Paget's disease of bone is due to direct inhibition of bone resorption by mithramycin or to the action of excess parathyroid hormone produced as a result of mithramycin-induced hypocalcaemia.

Parathyroid hormone normally increases bone destruction (Barnicot, 1948), but in view of the fall in urinary hydroxyproline the destructive effect of parathyroid hormone on

bone must in some way be inhibited by mithramycin. There is some evidence that parathyroid hormone also has an anabolic effect on bone, and Kalu *et al.* (1970) demonstrated a 23·5% increase in bone calcium, a 21% increase in stable hydroxyproline, and a 12·9% increase in incorporation of ^{3}H-proline into bone hydroxyproline in thyroparathyroidectomized rats treated with parathyroid hormone. This anabolic effect of parathyroid hormone on bone may be of importance if its destructive effect is simultaneously blocked by mithramycin.

The metabolic effects of mithramycin on calcium and phosphorus metabolism appear to be similar to those of calcitonin, which is known to be of therapeutic use in Paget's disease of bone. Calcitonin, like mithramycin, inhibits bone resorption and reduces plasma calcium in patients with Paget's disease of bone (Bijvoet *et al.*, 1968). There is presumably increased production of parathyroid hormone secondary to calcitonin-induced hypocalcaemia, and it may well be that both mithramycin and calcitonin exert their beneficial effect in Paget's disease of bone by a similar mechanism.

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Effect of Actinomycin D on Paget's Disease of Bone

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Summary

Four patients with active Paget's disease were treated with the RNA inhibitor actinomycin D. Three were clinically improved after treatment; the fourth had multiple collapsed vertebrae and showed no symptomatic improvement. Striking changes took place in urinary calcium and hydroxyproline, in serum alkaline phosphatase, and to a less extent in serum calcium and phosphate. These studies are continuing and are being compared with the effects of mithramycin.

Introduction

The RNA inhibitors best known in clinical use are mithramycin and actinomycin D. Both are derived from species of *Streptomyces*, and their most important place in medicine has been in the treatment of various testicular and renal tumours (Tan *et al.*, 1959; Brown and Kennedy, 1965). They are thought to exert their action by binding with the DNA chain, preventing RNA reduplication and thus blocking the synthesis of proteins and enzymes (Kirk, 1960).

It was noted during the trials of mithramycin that among its side effects hypocalcaemia was prominent (Parsons *et al.*, 1967). This prompted Ryan and Schwartz (1969) to study the effects of mithramycin in Paget's disease of bone. Their results indicate an improvement in the biochemical and clinical signs of the condition. They concluded that the effect of actinomycin D is "slight and transient," though no figures were quoted.

The purpose of this communication is to present four cases of Paget's disease treated with actinomycin D.

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Patients and Methods

The salient features of the four patients treated are shown in Table I. The three women were postmenopausal; the other patient was a 47-year-old bachelor. All had complaints of bone pain related to Paget's disease and were in hospital. They were maintained on a general ward diet which did not contain an excess of gelatin. Full blood counts and serum enzyme studies (serum aspartate aminotransferase, serum alanine aminotransferase, and serum lactate dehydrogenase) were carried out during treatment and for several weeks afterwards. Actinomycin D was administered into the tubing of a 5% dextrose infusion to a total dose of 2,500 µg over three to five days. Twenty-four-hour collections of urine were

TABLE I—*Clinical Features of Patients with Paget's Disease*

Case No.	Age	Sex	Distribution	Alk. Phos.	Symptoms
1	65	F	Skull, spine, pelvis	120	Back pain and deafness
2	62	F	Left pelvis	57	Leg pain
3	47	M	Skull, spine, pelvis	320	Back pain
4	75	F	Skull, spine	306	Headache, buzzing, deafness