Mithramycin in Paget's Disease

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SUMMARY

Mithramycin, a cytotoxic agent, has been used to treat 6 patients with severe symptomatic Paget's disease of bone. Bone pain improved dramatically. Side-effects included hypocalcaemia and nausea, but were not serious. Mithramycin is valuable in selected cases of Paget's disease.

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Paget's disease (osteitis deformans) is a relatively common disorder of bone, affecting 11% of persons over the age of 80 years in certain countries.[1] The majority of cases are asymptomatic but the occurrence of severe bone pain, progressive deformity, pathological fractures and sarcomatous changes, necessitates treatment. Until recently treatment has been largely limited to analgesics with little regard to the correction of the underlying defects, which include excessive osteoclastic activity destroying normal bone.

Mithramycin, a cytotoxic agent derived from an actinomycete of the *Streptomyces* genus, inhibits DNA and RNA synthesis as well as skeletal metabolism. It was originally successfully used in the treatment of testicular tumours[2] and hypercalcaemic states.[3] It was then shown to improve the clinical and biochemical features of Paget's disease, probably by inhibition of osteoclasts.[4] We have encountered 6 patients with gross, widespread Paget's disease with severe bone pain, in whom we decided to observe the effects of mithramycin. The study was not double-blind and did not include comparison with other therapy.

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PATIENTS AND METHODS

Six patients were admitted to Groote Schuur Hospital suffering from severe bone pain with radiologically, clinically and biochemically proved osteitis deformans. This pain in each case was sufficient to disrupt the patient's daily life, and prevent sleeping and having full mobility. It was only partially and temporarily relieved by previous therapeutic attempts in 5 of the 6 patients (patient 5 had not been administered any therapy). There was no associated hepatic, haematological or renal abnormality as determined on the 12/60 AutoAnalyzer and Coulter counter. Mithramycin (kindly supplied by courtesy of Pfizer Pharmaceuticals), was administered intravenously in a dose of 15 μg/kg body mass over 4 hours in 1 litre of 5% dextrose water solution. This dose was given daily as a course for 5 days. Further courses were given only if the patient failed to improve on the first course. No patient received more than 3 courses. The patients were

seen daily during their hospital stay, one month after discharge and then every 3 months as far as possible. Two patients, Nos. 4 and 6, were seen only twice after discharge as they had been referred from distant hospitals. At each visit a repeat 12/60 'auto-analysis' was performed. During each course of therapy, daily measurement of serum prothrombin, platelets, liver enzymes, creatinine, calcium, phosphorus and alkaline phosphatase were determined.

Where possible urinary calcium and hydroxyproline were measured. A rise in serum creatinine, liver enzymes, bilirubin, and a fall in platelets, white cells or prothrombin index would have been considered indications for stopping therapy.

RESULTS

The symptomatology, radiological involvement and previous medication of each patient is shown in Table I. All 6 patients experienced a reduction of pain (Table III), and in 3 this was dramatic. Mobility was improved in 2 patients (Table III), 1 of whom could discard the use of a wheelchair (patient 2). The failure to restore mobility in the others was probably related to secondary osteoarthritic changes of the neighbouring joints.

Side-effects (Table III) were limited to nausea. In 1 patient this was so severe that despite anti-emetics, therapy had to be discontinued. In patient 6 (Table III) pain was, however, dramatically relieved after 3 days of treatment. In the other 5 patients nausea was transient and mild. The biochemical changes were less striking than the improvement in pain. In all patients the alkaline phosphatase decreased during follow-up (Table IV). Except in patient 4, this fall was not sustained, and at the end of 3 months the alkaline phosphatase had returned to pretreatment values (Table II). A drop in serum calcium occurred in every patient, the lowest value (not shown on Table) being 6,9 mg/100 ml. At no stage did patients manifest tetany or paraesthesia. This asymptomatic hypocalcaemia was self-limiting, and 1 month after treatment 4 patients were normocalcaemic (9 - 11 mg/100 ml).

TABLE I. SYMPTOMATOLOGY, X-RAY FINDINGS AND PREVIOUS MEDICATION OF PATIENTS RECEIVING MITHRAMYCIN

Patient	Pretreatment symptoms	Radiological involvement	Previous medication
1 White female aged 72 years	Headache; deafness; painful hip movement; backache	Pelvis, left femur, lumbar spine, skull, osteoarthritis of left hip	Phosphate; fluoride; diazepam (Valium); dextropropoxyphene (Doloxene)
2 Coloured male age 59 years	Back pain; right hip pain; difficulty in walking	Skull, left side of pelvis, including hip, lumbar spine	Ibuprofen (Brufen); paracetamol (Panado); phenylbutazone
3 White female aged 70 years	Deafness; back pain; bilateral hip pain	Skull, pelvis, right and left femora, right humerus	Paracetamol (Panado); dipipanone hydrochloride (Wellconal); pethidine
4 White male aged 63 years	Headache; pain in legs	Skull, pelvis, right and left femora, lower dorsal vertebrae	Thyrocalcitonin; aspirin; paracetamol (Panado)
5 White male aged 54 years	Pain in left leg	Right pelvis, right femoral head, upper 2/3 left tibia, uper 2/3 right humerus	Nil
6 White male aged 63 years	Deafness; headache; back pain	Skull, lumbar spine, right and left tibia and femora	Ibuprofen (Brufen)

TABLE II. PRETREATMENT BIOCHEMISTRY OF PATIENTS WITH PAGET'S DISEASE

Patients	Alkaline phosphatase (N=14 - 85 IU)	Serum calcium (N=9 - 11 mg/100 ml)	Serum phosphorus (N=2,5 - 4,5 mg/100 ml)	Urinary calcium (N=± 240 mg/24 h)	Urinary hydroxyproline (N=<50 mg mg/24 h)
1	722	10,0	3,6	330	—
2	>700	9,1	3,1	302	—
3	>700	9,7	4,4	125	168
4	562	10,5	3,7	280	—
5	291	9,7	3,3	240	59,1
6	>700	9,4	3,6	127	—

TABLE III. POST-TREATMENT OBSERVATIONS OF PATIENTS WITH PAGET'S DISEASE

Patient	Pain	Mobility	Side-effects
1	Improved	Still impaired as severe osteo-arthritis of right hip	Nil
2	Much improved	Walked without difficulty	Nausea on day 1 of administration
3	Much improved	Improved	Nausea on day 1 of administration
4	Improved	No improvement	Nausea on day 4 of administration
5	Improved	No improvement	Nil
6	Much improved	Had no limitation originally	Severe nausea—necessitating termination of therapy after 3 days

TABLE IV. POST-TREATMENT BIOCHEMISTRY OF PATIENTS WITH PAGET'S DISEASE

	Alkaline phosphatase (N = 14 - 85 IU)			Serum calcium (N = 9 - 11 mg/100 ml)			Serum phosphorus (N = 2,5 - 4,5 mg/100 ml)			Urinary calcium (N = ±240 mg/24 h)			Urinary hydroxyproline (N = <50 mg/24 h)		
Patient	5 days†	1/12‡	3/12‡	5 days	1/12	3/12	5 days	1/12	3/12	5 days	1/12	3/12	5 days	1/12	3/12
1*	713	554	>700	8,8	8,0	9,5	3,0	2,9	3,9	213	—	—	—	—	—
2	>700	320	>700	8,6	10,1	9,5	3,9	3,4	3,4	80	—	—	—	—	—
3*	417	512	691	10,5	8,1	10,2	4,5	2,4	4,1	35	39	—	105	—	—
4	422	256	375	7,2	9,5	9,4	2,4	3,4	4,5				160	—	97,5
5	268	326	373	8,9	10,1	9,9	3,2	4,2	4,1	128	—	—	—	—	—
6	>700	482	>700	9,3	10,1	9,4	2,4	3,1	3,6					12,7	151

* More than 1 course. † 5 days postinfusion. ‡ 1/12 = 1 month postinfusion; 3/12 = 3 months postinfusion.

At the end of the 3 months all were normocalcaemic (Table IV). Urinary hydroxyproline was estimated in only 3 patients, and showed a decrease in 2 at some stage during the study. Urinary calcium excretion fell in 4 patients after 5 days' treatment (Table IV). No changes in hepatic and renal function or in blood count were observed.

DISCUSSION

The most striking benefit derived from the use of mithramycin in Paget's disease was the relief of bone pain, and to a lesser extent, return of mobility. Other workers have shown a decrease in the various indices of bone turnover, e.g. hydroxyprolinuria and serum alkaline phosphatase, to normal or near normal values while on treatment and for a limited period thereafter. X-ray films of the affected bone have also shown improvement.[6] In our study alkaline phosphatase decreased transiently but rose to pretreatment levels soon after stopping therapy. That this fall in alkaline phosphatase was so brief may have been due to the relatively short course that was given to each patient. Perhaps prolonged low-dose mithramycin on an outpatient basis is required to restore normality of bone turnover; such a scheme is being investigated elsewhere.[5] We observed a considerable, though transient, fall in serum calcium levels. This hypocalcaemic property of mithramycin has been used to treat resistant hypercalcaemia.[3]

Other agents used in the treatment of Paget's disease include thyrocalcitonin (TCT),[7] and the diphosphonates.[8] Thyrocalcitonin, which inhibits bone resorption, is expensive and requires prolonged treatment with daily or weekly intramuscular injections. The development of neutralising antibodies to porcine or salmon thyrocalcitonin has also handicapped the therapeutic benefit of this hormone. Human TCT is not commercially available but appears promising in this condition, and Woodhouse *et al.*[7] have observed progressive symptomatic and radiological improvement from its use. Disodium editronate (EHDP), a diphosphonate, slows bone turnover rate in experimental animals, and has been used in Paget's disease to reduce the excessive resorption and remodelling of bone. However, impaired mineralisation of osteoid tissue in normal and diseased bone has been seen with this compound; and the effect of smaller doses is still being investigated.[8]

We suggest that mithramycin be used in selected cases of Paget's disease, provided bone pain is the major symptom and no contra-indications to its use are present. The hypocalcaemic side-effect of this drug may also be beneficially employed as an emergency therapy in resistant life-threatening hypercalcaemic situations.

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