Acta orthop. scand. *50*, 33–38, 1979

MYOSITIS OSSIFICANS PROGRESSIVA

Clinical and Metabolical Observations in a Case Treated with a Diphosphonate (EHDP) and Surgical Removal of Ectopic Bone

H. HOLMSEN*, S. LJUNGHALL† & T. HIERTON*

Departments of Orthopedic Surgery* and Internal Medicine†, University Hospital, Uppsala, Sweden

A 20-year-old woman with a severely crippling myositis ossificans progressiva was treated with a diphosphonate (EHDP), 10–20 mg/kg/day. While being treated with this drug, surgical removal of ectopic bone was performed. Although ectopic calcification recurred postoperatively, considerable functional improvement was achieved. At the highest dosage of EHDP, hypercalcaemia gradually appeared, but was reversible upon cessation of drug treatment. It is probably related to a direct effect of EHDP on the bone.

Key words: diphosphonate (EHDP); metabolism; myositis ossificans progessiva; surgery

Accepted 8.viii.78

Myositis ossificans progressiva (MOP) is a rare disorder characterized by ectopic ossification occurring mainly in the connective tissue of muscle and joints. Calcification appears spontaneously or after trauma and certain infections. Widespread involvement produces a crippling illness in young people. Skeletal abnormalities, particularly of the toes and fingers, are also part of the clinical picture. Hereditary factors are probably involved but the mode of inheritance has not been established. Blood chemistry is normal and calcium balance studies are generally unremarkable (Smith et al. 1976).

Many therapeutic regimens have been tried and advocated including cortisone (Eaton et al. 1957), ACTH (Dixon et al. 1954) or measures to prevent mineralization, such as the use of calcium chelating agents or dietary restriction of calcium (Davis & Moe 1959). None have, however, been effective until the recent use of diphosphonate in several patients (Geho & Whiteside 1973). These compounds, among which the most widely used is disodium ethane-1-hydroxy-1,1-diphosphonate (EHDP), prevent the formation and dissolution of apatite crystals *in vitro*. In experimental animals they prevent both ectopic calcification (Fleisch et al. 1970) and excessive bone resorption and turnover (Gasser et al. 1972). In patients with MOP, therapy with EHDP has been used to prevent mineralization of areas of active myositis (Bassett et al. 1969, Weiss et al. 1971, Schnakenburg et al. 1972, Smith et al. 1976) or to prevent recurrence after surgical removal of established ectopic bone (Russel et al. 1972). The exact mechanism of their action is not known and it is possible that they may have an additional important effect on bone cells, either directly or indirectly, by reducing their activity. The main side effects, observed in a few patients, have been an inhibition of normal bone mineralization, pre-

0001–6470/79/010033–06$02.50/0

sumably due to an inhibition of vitamin D metabolism (Baxter et al. 1974).

In this report we present a case of MOP treated by surgical removal of ectopic bone under an "umbrella" of EHDP medication. During long-term therapy hypercalcaemia developed, but was reversible upon cessation of the drug treatment.

CASE REPORT

A 20-year-old woman was admitted to the Orthopaedic Department in 1975 because of severely crippling MOP. On admission she exhibited the characteristic congenital foot and hand abnormalities (Figure 1) and had experienced acute episodes of pain and swelling within the muscles since the age of three. Ectopic calcification had been particularly pronounced after surgery (because of a persistent ductus arteriosus), physical therapy and after a minor traffic accident. She was found to have a complete ankylosis of both hip joints – sitting in a wheelchair with a 90 degree flexion and 10 degree adduction contracture of both hip joints. There was markedly reduced mobility of the cervical and thoracic spine and no respiratory thoracic movements. Reduction of the mobility of the humeroscapular joints was also present as well as mandibular immobility. X-ray disclosed widespread ectopic calcification mostly around the hips (Figure 2), scapulae and spine.

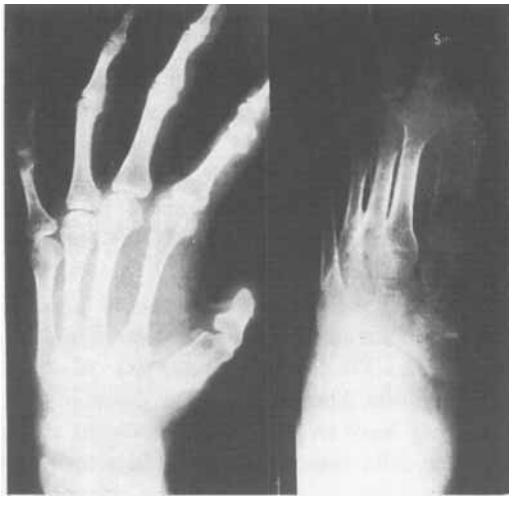
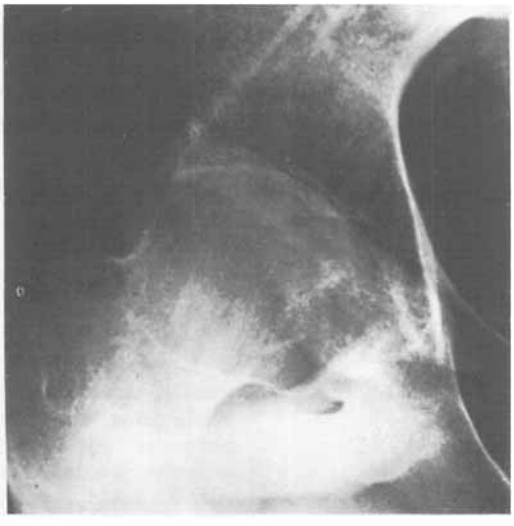
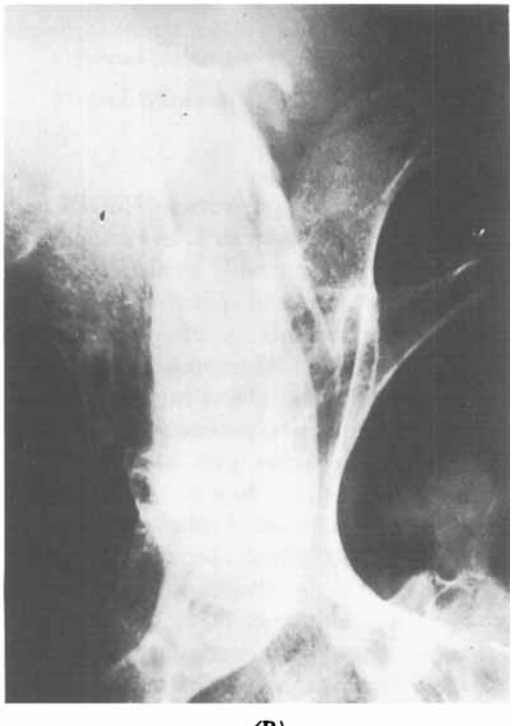


Figure 1. Radiographs of left hand and foot showing typical skeletal abnormalities.

Routine biochemical evaluation revealed nothing in particular except a moderate hypochrome anaemia. The serum concentrations



(A)



(B)

Figure 2. Radiograph showing extensive ectopic calcification around both hips. There is a solid bone bridge posteriorly between the femur and the ischium on the right side (A). On the left side the ectopic bone is in the front of the joint (B).

Table 1. Biochemical findings before, during and after therapy with EHDP in a case of myositis ossificans progressiva (normal ranges within parentheses)

	Before therapy	On therapy 2 months	On therapy 6 months	On therapy 12 months	After therapy
Serum calcium, mmol/l (2.20–2.60)	2.55	2.50	2.45	2.80	2.55
Serum phosphate, mmol/l (0.76–1.44)	0.9	1.4	1.4	2.1	1.4
Serum alkaline phosphatase, μkat/l (0.8–4.8)	3.3	3.3	4.1	5.1	3.3
Urinary calcium, mmol/24 h (0.6–5.0)	1.5	3.0	3.0	1.5	
Urinary hydroxyproline mg/24 h (6–22)	30	13	33		
Fractional intestinal calcium absorption, % (35–65)	85	50			
Serum parathyroid hormone, ng/ml	2.3			1.8	
Dose of EHDP, mg/kg/day	—	10	10	20	

of calcium, phosphate, alkaline phosphatase and creatinine were all within the normal range as were determinations of parathyroid hormone and calcitonin (Table 1). The urinary excretion of calcium was at the lower end of the normal range. Measurement of the intestinal calcium absorption, using an isotope technique (Ljunghall et al. 1977), indicated a high fractional uptake of calcium. The urinary hydroxyproline excretion on a collagen-free diet was normal. Therapy with EHDP (Procter and Gamble Company) was started with an initial dosage of 10 mg/kg/day. On this dose there was a significant increase in the serum phosphate concentration, while the serum calcium and alkaline phosphatase remained constant. The intestinal calcium absorption was reduced and the urinary calcium increased (Table 1).

The aim of our treatment was primarily to reduce the fixed deformity of both hip joints and if possible make the patient able to stand and to walk. EHDP was given in an attempt to suppress recalcification and make a surgical removal of ectopic bone worthwhile.

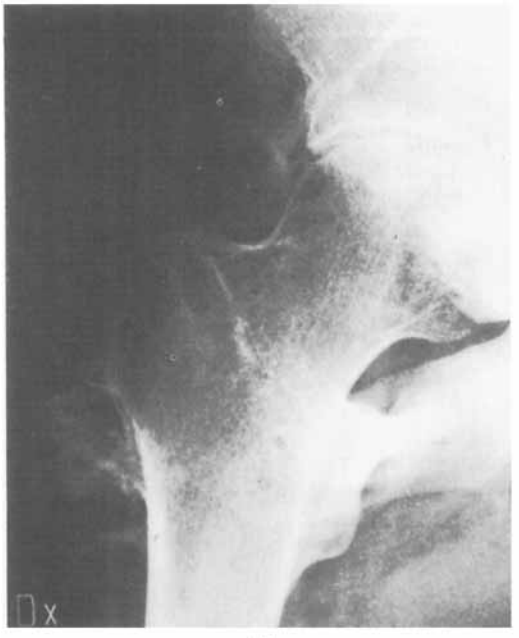
After 2 months of uneventful drug treatment surgical removal of ectopic bone around the hips was performed. Postoperatively the patient experienced markedly increased mobility and 3 weeks after the last operation done on the left hip joint the maximum range of movement was 25 degrees in the right and 40 degrees in the left hip joint and she was mobilized with crutches. After another 2 months, however, progressive limitation of hip mobility occurred. X-ray showed reappearance of calcification which gradually became as dense as before in spite of an increasing dosage of EHDP (Figure 3).

One year after institution of the therapy both hip joints were again ankylotic, but this time there was 35 degrees flexion and 10 degrees abduction of the right hip and 20 degrees flexion and 5 degrees abduction of the left hip. Furthermore, a restriction of the movement of both knee joints was noticed and the right ankle joint was ankylotic. However, the patient was still able to stand and to walk some 50 meters with the use of two sticks.

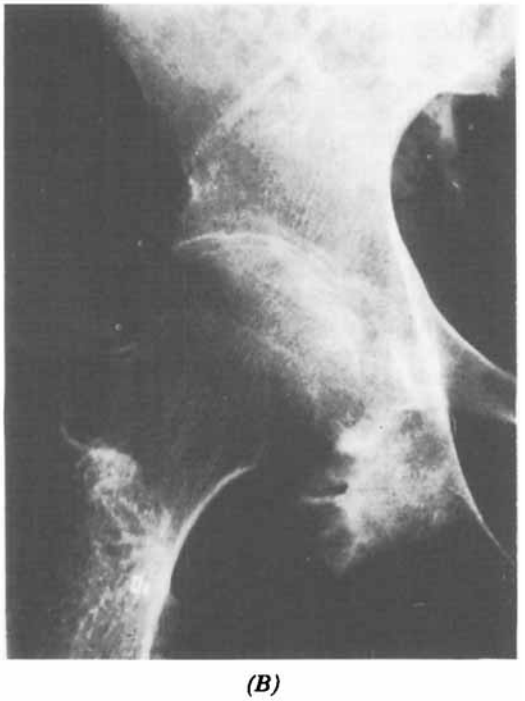
When the EHDP dosage was increased, the serum phosphate rose further and the serum calcium concentration also increased up to frank hypercalcaemia (Table 1). When therapy was stopped the serum calcium was 2.8 mmol/l but 2 weeks later both the serum calcium and phosphate concentration had returned to the pretreatment levels.

DISCUSSION

The first studies concerning the effects of EHDP in MOP reported considerable improvement in most of the patients, particularly as regards prevention of



(A)



(B)

Figure 3. Radiographs of the right hip joint: (A) 2 weeks after excision of ectopic bone bridge. (B) 2 years postoperatively there is reappearance of ectopic bone.

recurrence of ectopic bone after surgery. A positive attitude towards operative corrections followed. Now more experience has been accumulated and it appears that probably only about half of all MOP patients benefit from this treatment (Smith et al. 1976). The reasons for the variability of response are not known but there appears to be a dose-dependent relationship and a decreased absorption of the drug has been suggested as one possible mechanism of therapeutical failure. A high activity of the disease also appears to be an unfavourable prognostic sign. Unfortunately, at the present time, there seems to be no particular features recognized that can be applied to predict the outcome of surgical and medical therapy in the individual patient. In the present case the disease had been apparently quiescent for some years. Despite the use of a rather high dose of EHDP (10–20 mg/kg/day), yielding a substantial rise in the serum phosphate concentration and indicating an adequate intestinal absorption of the drug, there was little beneficial effect. Recurrence of calcification thus appeared within weeks of the operation. However, in spite of para-articular recalcification of both hip joints and a postoperative limitation of the movement in both knee joints, the treatment brought about an improved position of the ankylosed hips and facilitated standing and some walking (Figure 4). This improvement was greatly appreciated by the patient.

Some biochemical events merit further discussion. The intestinal calcium absorption, initially high, was reduced during the treatment period. Such a decrease has also been observed in experimental animals (Morgan et al. 1971) and children (Uttley et al. 1975), whereas conflicting data have been presented on the effects of EHDP on calcium absorption in adults (Walton et al. 1974). The observed reduction has been presumed to be the result of an interference with the normal vitamin D metabolism and can be corrected with small doses of active vitamin D (Bonjour et al. 1973a).

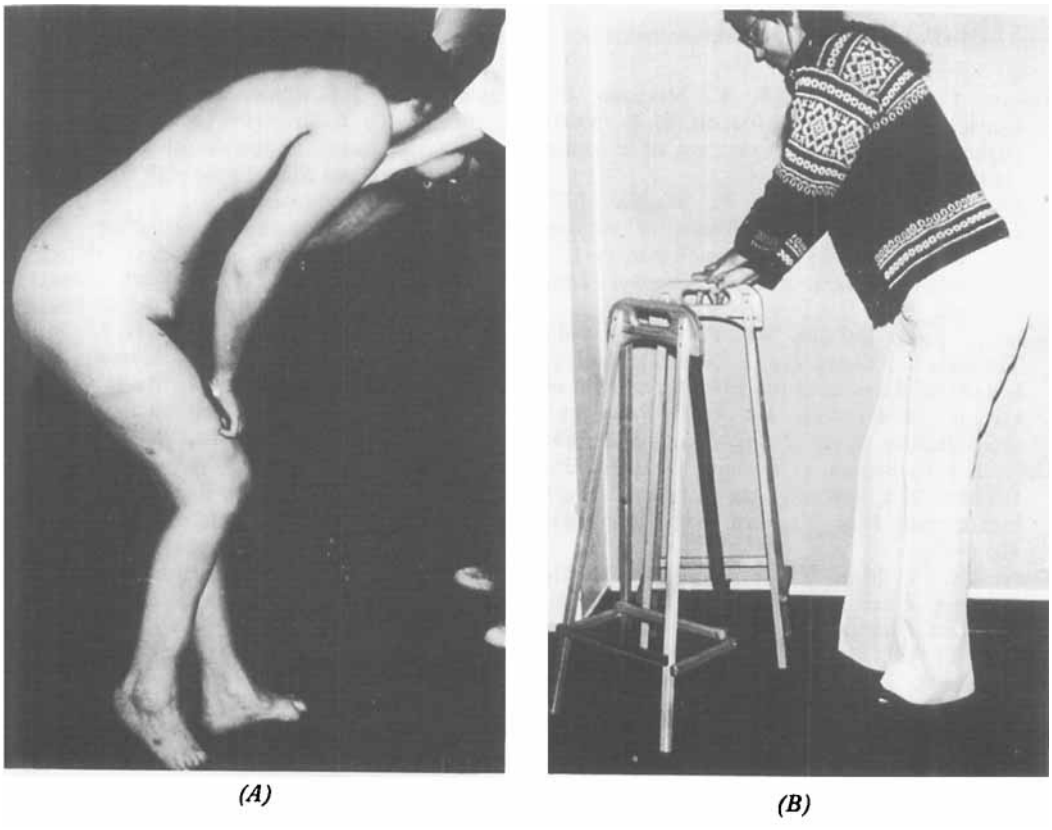


Figure 4. Photographs showing the patient's position (A) preoperatively (B) 2 years postoperatively.

Hypercalcaemia has, to our knowledge, previously been observed only in experimental animals on a much higher dose of EHDP than in the present case (Bonjour et al. 1973b). In our patient, however, hypercalcaemia appeared shortly after the EHDP dosage was increased and disappeared within days of the withdrawal of the drug. Thus, there was a clear relationship between the treatment and the hypercalcaemia. As the intestinal or renal handling of calcium did not change in the direction of increasing the serum calcium concentration it seems reasonable to suggest that the hypercalcaemia was related to the effect of EHDP on the mineralization process although not of the magnitude to cause a frank mineralization defect of normal bone.

In this disorder, where the underlying cause remains unknown therapeutic progress is likely to be small. However, the advantage of a relatively small increase in mobility or a more functional position of a fixed joint in a young patient, as in our case, can be worthwhile. Our own limited experience is not favourable as regards the effect of EHDP on ectopic bone formation. However, it is apparent from several studies that within the group of diphosphonates there are differences between the various compounds (Lemkes et al. 1977). Possibly therefore further research will provide new analogues, for example, with a more selective action on ectopic calcification, and with limited side effects, thus making the drug more useful in clinical practice.

REFERENCES

Bassett, C. A. L., Donath, A., Macagno, F., Preisig, R., Fleisch, H. & Francis, M. D. (1969) Diphosphonates in the treatment of myositis ossificans. *Lancet* **ii,** 845.

Baxter, L. A., DeLuca, H. F., Bonjour, J.-P. & Fleisch, H. (1974) Inhibition of vitamin D metabolism by ethane-1-hydroxy-1,1-diphosphonate. *Arch. Biochem. Biophys.* **164,** 655–662.

Bonjour, J.-P., DeLuca, H. F., Fleisch, H., Trechsel, U., Matejowee, L. A. & Omdahl, J. L. (1973a) Reversal of the EHDP inhibition of calcium absorption by 1,25-dihydroxy-cholecalciferol. *Europ. J. clin. Invest.* **3,** 44–48.

Bonjour, J.-P., Fleisch, H. & Copp, D. H. (1973b) Influence of a diphosphonate on serum calcium homeostasis. *Proc. Soc. exp. Biol. Med.* **143,** 404–407.

Davis, H. & Moe, P. J. (1959) Favourable response of calcinosis universalis to edathamil disodium. *Pediatrics* **24,** 780.

Dixon, T. F., Mulligan, L., Nassim, R. & Stevenson, F. H. (1954) Myositis ossificans progressiva. *J. Bone Jt Surg.* **36**-B, 445–449.

Eaton, W. L., Conkling, W. S. & Daeschner, C. W. (1957) Early myositis ossificans progressiva occurring in homozygotic twins. A clinical and pathological study. *J. Pediat.* **50,** 591–598.

Fleisch, H., Russell, R. G. G., Bisaz, S., Muhlbauer, R. C. & Williams, D. A. (1970) The inhibitory effect of phosphonates on the formation of calcium phosphate crystals *in vitro* and on aortic and kidney calcification *in vivo*. *Europ. J. clin. Invest.* **1,** 12–18.

Gasser, A. B., Morgan, D. B., Fleisch, H. A. & Richelle, L. J. (1972) The influence of two diphosphonates on calcium metabolism in the rat. *Clin. Sci.* **43,** 31–45.

Geho, W. B. & Whiteside, J. A. (1973) Experience with disodium etidronate in diseases of ectopic calcification. *Clinical aspects of metabolic bone disease.* Ed. Frame, B., Parfitt, A. M. & Duncan, H. Excerpta Medica, International Congress Series no. 270, 506–511.

Lemkes, H. P. J. J., Reitsma, P. H., Frijlink, W. & Bijvoet, O. L. M. (1977) Pharmacology of diphosphonates; Reduction of mineralization disturbance and clinical trial with ADP. *Calcif. Tiss. Res.* **24,** Suppl. 55.

Ljunghall, S., Backman, U., Danielson, B. G., Johansson, G., Jung, B., Källsen, R., Wibell, L. & Wälinder, O. (1977) Mechanisms of hypercalciuria in recurrent renal stone formers. *Scand. J. Urol. Nephrol.*, Suppl 41, 77–96.

Morgan, D. B., Bonjour, J.-P., Gasser, A. B., O'Brien, K. & Fleisch, H. A. (1971) The influence of a diphosphonate on the intestinal absorption of calcium. *Israel J. Med. Sci.* **7,** 384–386.

Russel, R. G. G., Smith, R., Bishop, M. C., Price, D. A. & Squire, C. M. (1972) Treatment of myositis ossificans progressiva with a diphosphonate. *Lancet* **i,** 10–12.

Schnakenburg, K. V., Gross-Selbeck, G. & Wiedemann, H.-R. (1972) Zur Behandlung der Fibrodysplasia ossificans progressiva mit "Diphosphonat" (EHDP). *Dsch. med. Wschr.* **97,** 1873–1876.

Smith, R., Russel, R. G. G. & Woods, C. G. (1976) Myositis ossificans progressiva. Clinical features of eight patients and their response to treatment. *J. Bone Jt Surg.* **58**-B, 48–57.

Uttley, W. S., Belton, N. R., Syme, J. & Sheppard, H. (1975) Calcium balance in children treated with diphosphonates. *Arch. Dis. Childh.* **50,** 187–190.

Walton, R. J., Russel, R. G. G., Smith, R. & Warner, G. (1974) Some effects of disodium ethane-1-hydroxy-1,1-diphosphonate (EHDP) on calcium metabolism in man. *Clin. Sci.* **47,** 13–14.

Weiss, I. W., Fischer, L. & Phang, J. M. (1971) Diphosphonate therapy in a patient with myositis ossificans progressiva. *Ann. intern. Med.* **74,** 933–936.

Correspondence to: Dr Sverker Ljunghall, Department of Internal Medicine, University Hospital, S-750 14 Uppsala, Sweden