Acta orthop. scand. 45, 926–934, 1974

Department of Clinical Endocrinology and Metabolism, University Hospital, Leiden and Department of Orthopaedics, Catholic University, Nijmegen, The Netherlands.

EFFECT OF A DIPHOSPHONATE ON PARA-ARTICULAR OSSIFICATION AFTER TOTAL HIP REPLACEMENT

O. L. M. Bijvoet, A. J. G. Nollen, T. J. J. H. Slooff & R. Feith

Accepted 8.iv.74

In recent years para-articular ossifications have been recognized with increasing frequency as a complication of total hip alloarthroplasty (Wilson et al. 1972, Patterson & Brown 1972, Nollen & Slooff 1973). These ossifications first become visible on low kilovoltage X-rays 2 to 3 weeks after surgery as ill-defined opacifications of mottled appearance in the gluteal and/or psoas region. With time they may develop into bony bridges between the femur and pelvis. Their appearance is often associated with pain and slight swelling of the hip without redness, fever or signs of infection and may occasionally, over a period of 12 weeks, lead to severe limitation of passive and active hip movement. Some degree of ossification was seen in about 50 per cent of our patients and severe loss of function occurred in 7 per cent (Nollen & Slooff 1973). Histologically the lesion resembles that seen in myositis ossificans and paraosteoarthropathy; it consists of normally mineralized osteoid and a woven bone structure which is remodelled to trabecular bone.

There is no known therapy, and hitherto no acceptable suggestions for treatment have been presented in the literature. Because of the resemblance to myositis ossificans and because it has been suggested that the diphosphonate EHDP (disodium ethane-1-hydroxy-1, 1-diphosphonate) retards mineralization of the ectopic bone matrix in myositis ossificans (Russell & Smith 1973), we investigated the effect of EHDP on the development of these para-articular ossifications.

PATIENTS AND METHODS

Patients

Forty-two patients suffering from hypertrophic osteoarthritis underwent hip alloarthroplasty. The surgical approach was anterolateral with a Müller-type prosthesis (4 patients) or posterolateral with a McKee-type prosthesis. Both types of prosthesis were cemented with Palacos® a bone cement on methylmethacrylate base (Kulzer-Cie., Bad Homburg, West Germany). The joint capsule was excised *in toto*. Postoperative care was the same for both groups of patients and consisted of wound drainage for 48 hours, a hip spica for 5 days and traction in abduction and extension for 5 days. Anticoagulants were given from the first postoperative day; isometric static exercises were also started at this time. Walking without weightbearing, with two English canes, was started 5 days after surgery. From the 10th postoperative day the patients did active hip exercises and exercises with weightbearing.

The patients were randomly divided into a group receiving EHDP (20 patients) and a control group (22 patients). The groups were comparable with respect to type of operation, sex and age distribution. The age in both groups averaged 65 years.

Experimental details

The experimental patients received 20 mg per kg per day of EHDP divided into three equal doses and administered orally 30 minutes before meals.

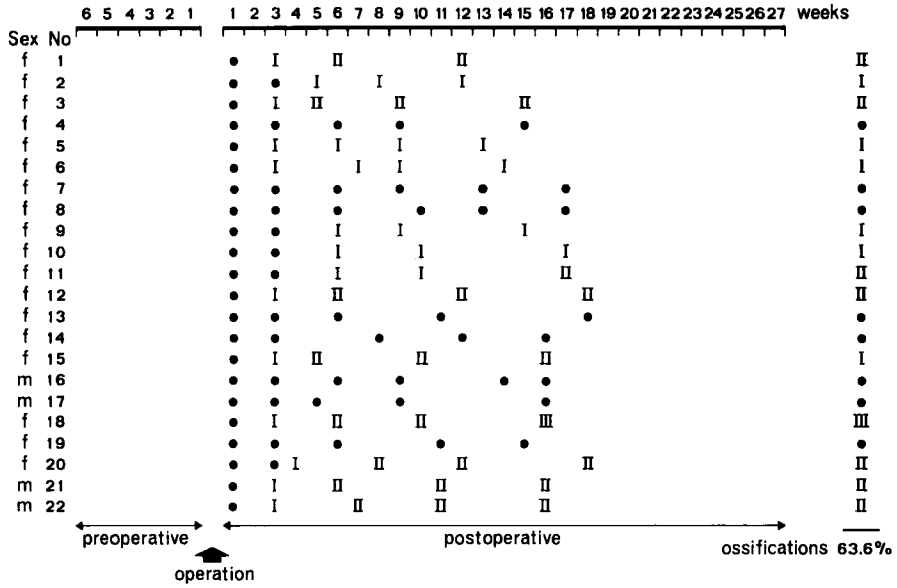

Figure 1. Development of ossifications after total hip replacement. Symbols at dates of low kV radiography refer to absence of ossification (closed circles) or presence of ossifications of grade I, II or III, respectively.

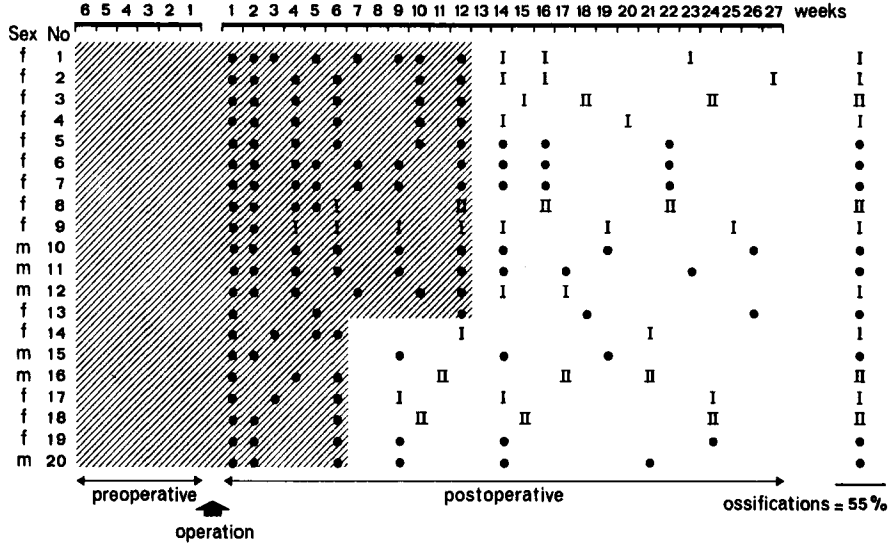

Figure 2. Development of ossifications after total hip replacement in EHDP-treated patients. Shaded area refers to period of treatment. For other symbols see legend to Figure 1.

Treatment was started 6 weeks before surgery and continued until the end of the sixth (7 patients) or twelfth (13 patients) postoperative week. In all patients low kV radiograms were made at regular intervals until approximately the 24th postoperative week (Figures 1 and 2), and assessed for the presence of ossification. Four grades of ossification were defined as follows:

grade 0 : no ossifications visible.
grade I : ossifications in gluteal area only, ill-defined and without distinct bony structure.
grade II : ossifications in gluteal and psoas regions, ill-defined but often having a more distinct structure.
grade III: complete bony bridges between femur and pelvis in gluteal and psoas regions with normal bone structure.

Joint mobility and pain were assessed immediately before and 6 months after surgery. Range of motion, expressed in degrees, was defined as the sum of mobility in the sagittal, frontal and rotational plane, and was used to describe the functional results. The results were then classified as good (100–200°), fair (50–100°) or poor (0–50°). In eight EHDP-treated patients, plasma creatinine (alkaline picrate method) and phosphate concentrations (Summer 1944) and renal phosphate reabsorption activity (Bijvoet et al. 1969) were assessed immediately before and six weeks after the initiation of treatment.

Six control patients allowed an iliac crest biopsy at the time of the operation and five EHDP-treated patients agreed to have this done at the time of the operation and at the end of treatment (three months after surgery). Undecalcified

Table 1. Effect of total hip replacement on pain and mobility in patients treated with EHDP and in controls.

Pain	improved	unchanged	worse
Control	17	5	0
EHDP	18	1	1
Joint mobility	**good (100–200°)**	**fair (50–100°)**	**poor (0–50°)**
Control before	4	11	7
after*	3	13	6
EHDP before	4	4	12
after**	17	3	0

* $P > 0.1$; ** $P < 0.001$.

sections were stained (Schenk 1965) and the volume percentage of cancellous bone consisting of uncalcified osteoid was assessed according to Merz & Schenk (1970). Student's t test was used to calculate the probability levels of the means and χ^2 for the fit of assumed distributions to actual data.

A systematic check on toxicity of EHDP included leucocyte and thrombocyte counts, examination of urinary sediment and protein excretion and measurements of serum alkaline phosphatase and 5-nucleotidase. No adverse effects were noted.

RESULTS

Development of ossification. (Figures 1 and 2) Thirteen out of 22 control patients developed visible ossification between 2 and 6 weeks after surgery. Only two out of 20 EHDP-treated patients developed visible ossification during the diphosphonate treatment, but two to three months after discontinuation of EHDP, ossifications had appeared in 11 out of 20 patients. They often became visible on radiograms taken 2 weeks after treatment was stopped. The difference between patients receiving EHDP and the control group was significant at 6 weeks ($P < 0.001$) and 12 weeks ($P < 0.01$). At 27 weeks ossification occurred equally in both groups ($P > 0.5$). There was an important subjective difference between the two groups. In contrast to the control group, the appearance of ossification after discontinuation of EHDP was never associated with pain or swelling of the hip in the treated patients.

At three weeks after surgery, the normal time for ectopic ossifications to become visible on X-rays, there was no significant rise of

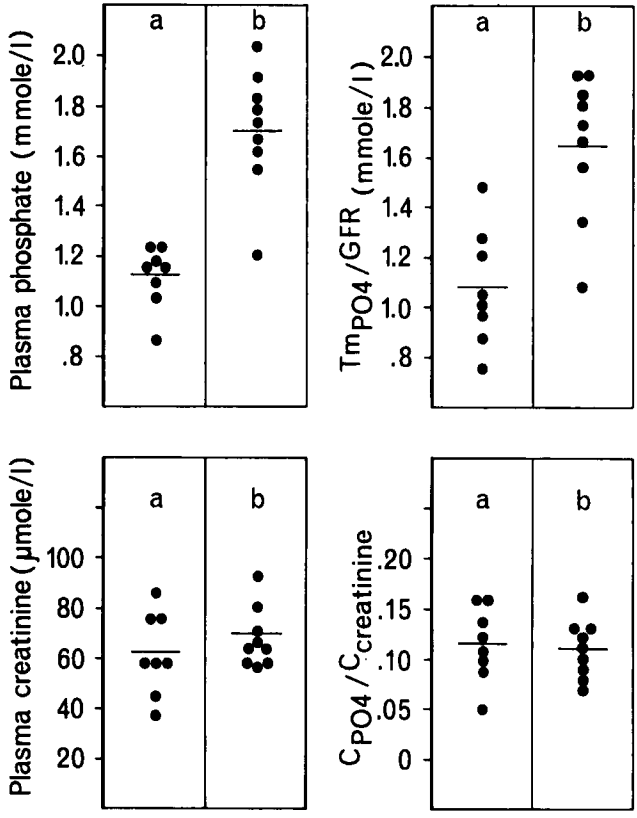

Figure 3. The fasting plasma phosphate concentration, phosphate reabsorption activity (Tm_{PO4}/G.F.R.), plasma creatinine concentration and the ratio of phosphate to creatinine clearance ($C_{PO4}/C_{creatinine}$) at the time of surgery, in control patients (a) and in patients pretreated for 6 weeks with EHDP (b).

serum alkaline phosphatase, creatinine phosphokinase (CPK), and lacticdehydrogenase (LDH) in either of the two groups.

Joint mobility and pain. (Table 1) Preoperative joint mobility was impaired to a similar extent in the control and the EHDP-treated group. Final mobility was significantly better in the EHDP group, whereas there was no overall improvement in the control group. Pain however was relieved in both groups to a similar extent.

The serum phophate concentration (Figure 3) increased significantly during EHDP treatment ($P < 0.01$). The elevation was due to an increase ($P < 0.01$) in the activity of renal tubular phosphate reabsorption (Tm/GFR). There was no associated change in glomerular filtra-

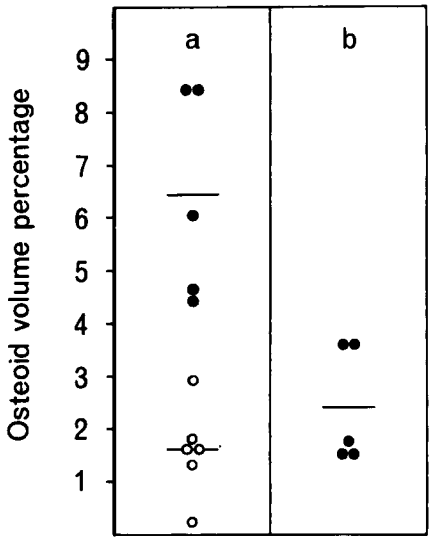

Figure 4. Osteoid volume percentage in iliac crest biopsy taken during the operation (a) and 3 months after surgery (b) in control patients (open circles) and in patients treated with EHDP (closed circles).

tion rate because serum creatinine concentrations remained unchanged ($P > 0.5$).

The ratio of phosphate to creatinine clearance did not change ($P > 0.5$) but it should now be well-known that this ratio in the presence of a changing serum phosphate does not offer useful information on tubular phosphate reabsorption (Bijvoet et al. 1969). Serum phosphate and renal tubular reabsorption of phosphate showed normal values again after the EHDP treatment was ended.

Iliac crest biopsies. (Figure 4) In iliac crest biopsies from treated patients, taken at the time of the operation (after 6 weeks of EHDP treatment), the percentage of bone volume consisting of uncalcified osteoid was considerably higher than in the control patients ($P < 0.01$). Surprisingly, in biopsies taken 3 months after surgery, when EHDP treatment had not yet been discontinued, the volume percentage had normalized ($P > 0.05$).

DISCUSSION

Diphosphonates may prevent soft-tissue calcification induced experimentally in animals (Fleisch et al. 1970). EHDP has been used in myositis ossificans progressiva to prevent progression in active cases and to prevent recurrence after removal of established extopic bone in adults. The results have recently been reviewed by Russell & Smith (1973). Their provisional conclusion is that there is no definite

evidence to show that such treatment causes either regression of established ectopic bone or increased mobility of joints not operated upon. When a joint in such patients is operated on there is no evidence that EHDP inhibits the reformation of the ectopic bone matrix itself but it may be effective in delaying the calcification of this matrix. There is no way to assess in these patients whether the delay in calcification has a beneficial effect on joint mobility.

The present study describes the effect of EHDP on a group of non-septic ectopic ossifications of the locomotor apparatus that are comparable to the ossifications around large joints occurring in myositis ossificans or in the so-called paraosteoarthropathies observed in association with paraplegia (Nollen & Slooff 1973). However in contrast to these conditions, the occurrence of para-articular ossifications in total hip replacement is sufficiently frequent and predictable to offer the opportunity of a controlled study and to allow quantitative assessment of results.

Our data demonstrate that continued administration of EHDP did significantly reduce the frequency of radiologically visible ossification after alloarthroplasty. The effect persisted for at least three months, the maximum duration of EHDP-treatment. However, the treatment did not affect the underlying lesions because ossifications became visible within a few weeks after discontinuation of treatment. We therefore conclude that EHDP-treatment does not prevent the formation of ectopic bone-matrix, but only delays the mineralization of this matrix. This effect can only be maintained by continuing the EHDP-administration, because when the drug was discontinued earlier than 3 months after surgery, ossifications reappeared earlier. The normal time for these abnormalities to appear in the controls was within 1 to 3 weeks after surgery. In contrast to the control patients, the appearance of ossification was not associated with pain in EHDP-treated patients.

The ultimate frequency of the occurrence of ossifications was not significantly different. However, there were two important differences between treated and control patients. Firstly, the treated patients did not experience pain. Secondly, the ultimate function of the hip of the treated patients was significantly better than that of untreated patients. In fact the functional results of alloarthroplasty were greatly improved and had become optimal. The reason for this may be that mineralization of the lesions had been delayed until after the patients were fully mobile and could exercise without pain.

The development of an excess of uncalcified osteoid is a recognized complication of EHDP-treatment and this was visible in our patients too. We cannot explain why after 18 weeks of treatment the amount of osteoid in the iliac crest biopsy was actually less than after 6 weeks whereas no calcification around the hip had occurred. Russell & Smith did not find evidence of a mineralization disorder in the bone of the normal skeleton of a patient with myositis ossificans treated with EHDP, who died six months after surgery, whereas tissue excised at the site of the operation showed only a partially mineralized matrix (Russell & Smith 1973). A possible explanation is that EHDP delays but does not prevent mineralization of newly formed normal bone and that the final reduction of the osteoid excess reflects a reduction of the rate of bone remodelling. The latter effect of EHDP may be responsible for its beneficial effect in Paget's disease.

The only other abnormality we found was an elevated serum phosphate concentration due to an increased renal tubular phosphate reabsorption in the kidney. This confirms the findings of Recker et al. (1973) who also reported that the renal tubules of EHDP-treated patients still respond normally to exogenous parathyroid hormone.

Since this study we have reoperated patients who after a period had experienced considerable loss of hip function due to ectopic ossification. Treatment with EHDP from 6 weeks before until 3 months after operation has resulted in optimal postoperative results. We conclude that treatment with EHDP, possibly in conjunction with adequate exercise, considerably increases the functional results of total hip replacement. Our results also suggest that even though EHDP does not prevent the recurrence of ossification after reoperation in myositis ossificans, there is hope that these patients may yet gain in mobility and that treatment of such patients need not be prolonged indefinitely when the disease is in a quiescent phase.

SUMMARY

Forty-two patients underwent total hip alloarthroplasty. Twenty of these patients were selected at random and received disodium ethane-1-hydroxy-1, 1-diphosphonate (EHDP) orally from 6 weeks before the operation until 6 (7 patients) or 12 weeks(13 patients) after surgery. Some degree of para-articular ossification developed in 13 out of 22 control patients. EHDP treatment delayed the radiological appearance of ossification but did not prevent its occurrence after treatment was

stopped. However the treatment did prevent impairment of mobility as a result of ossification and considerably improved the functional results of total hip replacement. These findings indicate that EHDP may also be an effective adjunct to surgical treatment in myositis ossificans. EHDP treatment raised the plasma phosphate concentration by increasing renal tubular phosphate reabsorption. Iliac crest biopsies showed development of excess uncalcified osteoid; this effect was however transient.

ACKNOWLEDGEMENTS

We thank Mrs. Ria Reynen for technical assistance and Henkel and Cie GmbH Düsseldorf for kindly donating EHDP.

REFERENCES

Bijvoet, O. L. M., Morgan, D. B. & Fourman, P. (1969) The assessment of phosphate reabsorption. *Clin. chim. Acta* **26**, 15.

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

Merz, W. A. & Schenk, R. K. (1970) Quantitative structural analysis of human cancellous bone. *Acta anat. (Basel)* **75**, 54.

Nollen, A. J. G. & Slooff, T. J. J. H. (1973) Para-articular ossifications after total hip replacement. *Acta orthop. scand.* **44**, 230.

Patterson, F. P. & Brown, C. S. (1972) The McKee-Farrar total hip replacement. *J. Bone Jt Surg.* **54**-A, 257.

Recker, R. R., Hassing, G. S., Lau, J. R. & Saville, P. D. (1973) The effect of disodium ethane-1-hydroxy-1, 1-diphosphonate (EHDP TM) on the kidney response to parathyroid hormone. *J. Lab. clin. Med.* **81**, 258.

Russell, R. G. G. & Smith, R. (1973) Diphosphonates. Experimental and clinical aspects. *J. Bone Jt Surg.* **55**-B, 66.

Schenk, R. (1965) Zur histologischen Verarbeitung von unentkalkten Knochen. *Acta anat. (Basel)* **60**, 3.

Sumner, J. B. (1944) A method for colorimetric determination of phosphorus. *Science* **100**, 413.

Wilson, P. D., Amstutz, H. C., Czernicki, A., Salvati, E. A. & Mendes, M. D. (1972) Total hip replacement with fixation by acrylic cement. *J. Bone Jt Surg.* **54**-A, 207.

Correspondence to:

T. J. J. H. Slooff
Department of Orthopaedics
St. Radboud University Hospital
Nijmegen, The Netherlands