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TREATMENT OF PAGET'S BONE DISEASE WITH A BISPHOSPHONATE

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Satisfactory results have been obtained with the use of calcitonin or disodium (1-hydroxyethylidene)-1,1 bisphosphonate (EHDP) in the treatment of Paget's bone disease. However calcitonin is expensive and must be administered parenterally. EHDP could inhibit bone mineralization when given in a dosage above 5 mg/kg [2, 8, 9, 17] and we have seen with increased frequency resistance to its action. New drugs that could circumvent the mentioned inconveniences have been investigated such as (3- amino -1- hydroxypropilidene)-1,1- bisphosphonate (APD) [4, 7] or dichloromethylidene bisphosphonate [14] of wich only the former will be considered in the present report. It was found in experimental studies that APD is 10 times more potent than EHDP to inhibit osteoclastic activity whereas the dose of APD needed to produce osteomalacia should be markedly higher than that required to inhibit bone resorption [3]. Frijlink et al [7] have reported the effects of APD administered initially in a dose of 8.16 mg/kg in 18 patients with osteitis deformans. Bone resorption became normal in approximately one week whereas there was a 3 to 6 month delay for return of bone formation to normal range. The present paper reports the clinical, laboratory and radiological effect of APD on 57 patients with Paget's bone disease.

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Materials and methods

A total of 29 women and 28 men with Paget's bone disease were studied. In 40 cases the disease was polyostotic and in 17 oligostotic. Average age was 66.1 with a range from 40 to 82 years. Eighteen patients had not received previously any antipagetic treatment whereas 39 patients had been previously treated with EHDP either alone or combined with calcitonin. APD was given initially in a dose of 8.0 to 8.5 mg/kg, divided in 3 doses ½ hour before meals. After 45 days of treatment the dose was reduced to 7.0 mg/kg.

Clinical assessment included all patients regardless of the length of treatment. Alkaline phosphatase (AP) [11] and urinary total hydroxyproline (THP) [13] were measured before treatment and every two months thereafter. Laboratory assessment included only those patients with a length of therapy of 4 or more months. The response was considered positive when both AP and THP decreased to 60 % or less of the initial values.

Roentgenological studies of the affected bones were performed every 2 to 6 months, although initially they were not done systematically in all patients.

Fisher exact test were performed to compare differences in proportions [20]. Laboratory data on dependent samples were compared by analysis of variance [18].

Results

Toxicity. Due to gastric intolerance treatment was interrupted in 7 patients (12.3 %). Two of them had not been previously treated (NPT) meanwhile five had previously received antipagetic therapy (PT). The difference was not statistically significant (Table 1). One patient

TABLE 1. — *Comparison of toxic effects of APD in non previously treated and previously treated groups of patients*

	Nº of patients	%	Intolerance	%
Non previously treated	18	31.6	2	11.1
Previously treated	39	68.4	5	12.8
Total	57		7	12.3

Fisher exact test: p = 0.33 not significant.

had a sudden peak of fever that lasted only one night. Hematological controls and liver enzymes did not disclose significant changes.

Bone pain (Table 2). This was assessed in 45 patients, since 8 patients were free of pain and 4 patients (77.8 %) were improved. The clinical amelioration was higher among the NPT patients (90.0 %) compared with the PT patients (74.3 %) but the difference between groups was not statistically significant (Table 3). Symptoms were unchanged in 6 (13.3 %) and became worse in 4 (8.9 %) patients, all of them in the PT group.

Biochemistry. This was assessed in 41 patients. A positive response was observed in 32 patients (78 %). In 91.7 % of the NPT group the response was positive whereas only 72.4 % of the PT patients had similar effective results but the difference between groups was not statistically significant (Table 3).

TABLE 3. — *Comparison of effects of APD on serum AP and urinary THP in non previously treated and previously treated groups of patients*

	Nº of patients	Positive response	%	Negative response	%
Non previously treated	12	11	91.7	1	8.3
Previously treated	29	21	72.4	8	27.6
Total	41	32	78.0	9	22.0

Fisher exact test: p = 0.16 not significant.

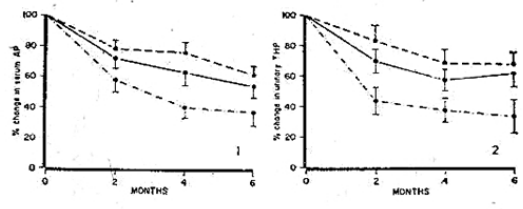
Alkaline phosphatase (Table 4, Fig. 1). A significant diminution of serum AP was observed after 2 months of APD in the whole group and in the 29 PT patients ($p < 0.005$). Thereafter, the small further decrease was not statistically significant. Likewise the fall in serum AP observed in the NPT group at 2 months was not significant. No significant differences were observed between the decrease of the whole group and the PT or NPT groups. The results expressed as a percentage of the initial values (Table 4) yielded conclusions similar to the ones obtained with the absolute values.

Urinary total hydroxyproline (Table 5, Fig. 2). After two months of treatment, a very significant decrease was observed in the entire group and in the PT patients

TABLE 2. — *Comparison of effects of APD on bone pain in non previously treated and previously treated groups of patients*

	Nº of patients	%	Improvement	%	No improvement	%	Worsening	%
Not previously treated	10	22.2	9	90.0	1	10.0	—	
Previously treated	35	77.8	26	74.3	5	14.3	4	11.4
Total	45		35	77.8	6	13.3	4	8.9

Fisher exact test: p = 0.32 not significant.



1 2

Figs. 1-2 — 1, Effect of APD on percent changes of serum AP in the whole group (—) previously treated (—) and non previously treated (—) group of patients; 2, Effect of APD on percent changes of urinary THP in the whole group (—) previously treated (—) and non previously treated (—) groups of patients.

($p < 0.001$). Thereafter a small and not significant further diminution was observed. A less significant decrease was found in the NPT patients. The fall observed when results were analyzed as percentage of the initial values (Table 5) disclosed significant differences at 2 months in the groups ($p < 0.001$). The other results were similar to the ones obtained.

Radiological changes. Definite increments in radiological bone density were observed in five well controlled patients. Two of them will be briefly reported.

Patient 1, a 66 year old white male, presented marked deformity and pain over the right humerus where he had three previous fractures. X-rays studies disclosed an osteitis with marked rarefaction (Fig. 3 A). He had received previously EHDP (7 mg/kg) during 17 months without appreciable changes. After 4 months of APD (8.3 mg/kg) the patient was clinically improved; serum AP decreased from 93 to 25 K.A. units and urinary THP from 93 to 43 mg per 24 hs. After 10 months of treatment, the X-ray of the humerus revealed marked increase of bone density (Fig. 3 B).

Patient 2, a 66 year old white female presented marked deformity of the long bones, mild bone pain and osteoporosis circumscripta cranii (Fig. 4 A). She had previously received EHDP (8 mg/kg) during 12 months, and the combination of EHDP (6 mg/kg) plus salmon calcitonin (64 units three times a week) during 4 months. After 8 months of APD (7 mg/kg), the serum AP diminished from 67 K.A. units to 43 K.A. to 257 K.A. units, the urinary THP from 336 to 257 mg per 24 hr. The X-ray studies showed increased density of the right humerus and of the skull with the osteoporosis circumscripta (Fig. 4 B).

Discussion

The results we have obtained with the use of ADP in the treatment of Paget's bone disease are somewhat similar to those previously reported [5, 7]. Some differences however deserve to be mentioned. Frijlink et al [7] obtained in their patients a more rapid and significant decrease to within normal limits of the biochemical indexes than the effects observed in the presently reported NPT patients. A different severity of the Paget's disease seems to be the most logical explanation. Average excretion of THP was approximately 1.6 times the upper normal limits in Frijlink's series whereas in our patients it was 6.0 times higher than the upper normal values. On the other hand, a good biochemical effect was observed in 72.4 % of 29 PT patients, who in the great majority were not responding

TABLE 4. — *Effects of APD on serum alkaline phosphatase (Serum AP)*

	Cases	Basal	Serum Ap Units * **		
			2 months	4 months	6 months
Whole group	41	85.8 ± 8.5	58.6 ± 7.2[a]	50.3 ± 6.5	46.7 ± 6.4
% from basal value		100	71.2 ± 5.5[a]	64.6 ± 4.8	54.3 ± 6.6
Previously treated	29	80.8 ± 7.6	61.1 ± 8.9[a]	54.2 ± 8.1	50.6 ± 7.4
% from basal value		100	77.7 ± 7.0[a]	76.1 ± 10.1	61.0 ± 7.1
Non previously treated	12	97.9 ± 22.8	53.5 ± 12.3	41.8 ± 10.8	36.0 ± 13.2
% from basal value		100	57.5 ± 7.6	39.6 ± 7.3	36.7 ± 7.5

* Average ± SE; ** Normal values: 5-15 K.A. units; [a], $p < 0.005$.

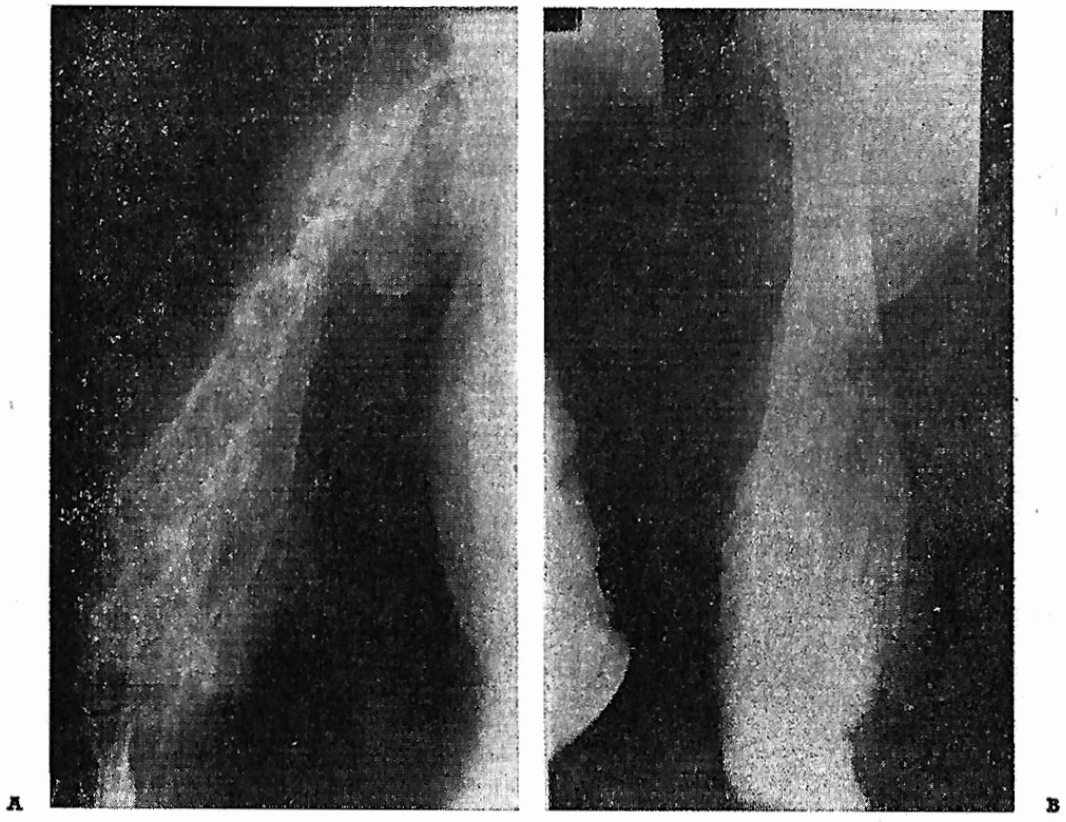


Fig. 3. — Case 1, A. Accentuated osteolytic form of trabeculated osteitis of right humerus that had suffered 3 previous fractures (December 18, 1980). B. Significant increased density after 10 months of treatment.

TABLE 5. — *Effects of APD on urinary total hydroxiproline (THP)*

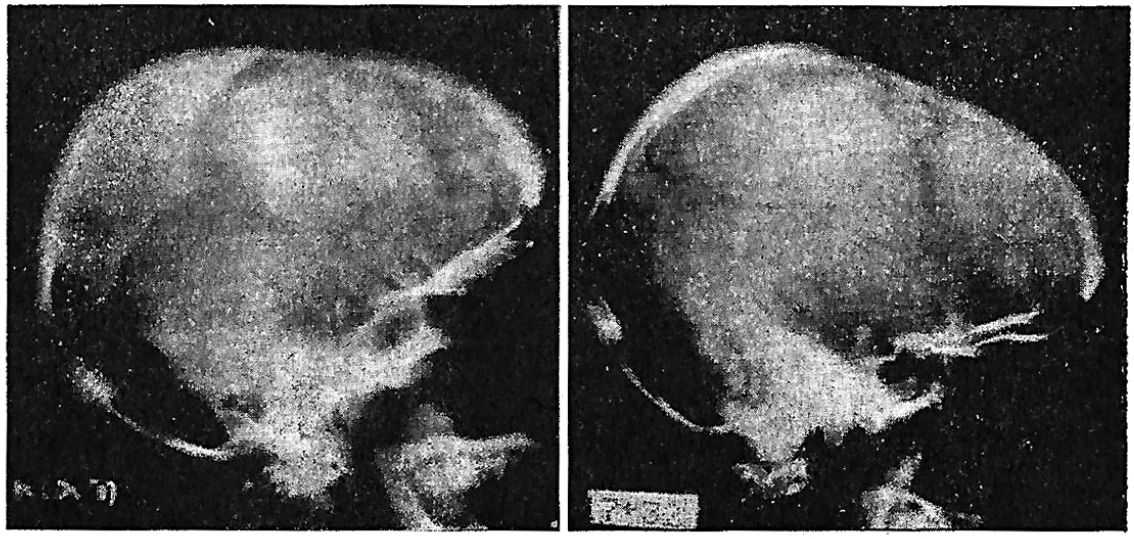
	Cases	Basal	THP mg/24 h * **		
			2 months	4 months	6 months
Whole group	41	179.2 ± 21.3	124.7 ± 17.7[a]	104.9 ± 16.7	112.9 ± 15.5
% from basal value		100	71.7 ± 6.5[a]	58.8 ± 5.5	61.6 ± 6.3
Previously treated	29	153.5 ± 20.2	124.3 ± 19.6[a]	105.2 ± 19.8	111.6 ± 14.2
% from basal value		100	82.8 ± 7.9[a]	69.6 ± 7.0	69.2 ± 6.8
Non previously treated	12	241.3 ± 51.4	125.7 ± 38.8	104.2 ± 31.4	117.8 ± 56.5
% from basal value		100	42.8 ± 6.5[a]	39.2 ± 5.6	32.8 ± 7.9

* Average ± SE; ** Normal values: 15-40 mg/24 hours: [a], $p < 0.001$.

to EHDP or in some cases did not tolerate calcitonin injections. Some distinction should be made between the PT and the NPT patients. The latter group apparently had a better clinical and humoral response although the difference was not evident in the statistical analysis.

The radiological improvement of bone mineralization and the repair of the osteolytic lesions verified in several patients is one of the favorable effects of APD. Bijvoet el al [5] had made similar observations that are attributed to the potent inhibitory effect of the drug upon bone resorption and the induction of a positive calcium balance [7].

Calcitonin [6] or less frequently EHDP [12, 15, 19] might produce improvement of the radiological lesions. The adverse reactions we have observed with the administra-



A B

Fig. 4. — Case 2, A. Extended osteoporosis circunmscripta cranii on January 22, 1981. B. Increased mineralization after 8 months of treatment.

tion of APD include: gastric intolerance (12.3 %), failure to induce a clinical remission and/or worsening of symptoms (22.2 %) and lack of a positive laboratory response (22.0 %). Bijvoet et al [3] and Nagant de Deuxchaisnes et al [16] observed in short term studies, extending to 9 and 5 days respectively, a transient decrease in the number of white cells and lymphocytes. These diminutions were apparently related to the initial fall in the urinary hydroxyproline excretion and the elevation of body temperature. A periodic hematological survey is presently performed in all our patients and will be reported elsewhere. Is should also be mentioned that Adami et al [1] and Nagant de Deuxchaisnes et al [16] observed in their patients receiving APD a significant diminution in the circulating levels of calcium and phosphate. The serum PTH was increased although this increment was not statistically significant in the study performed by Nagant de Deuxchaisnes. We have not observed any clinical manifestations of secondary hyperparathyroidism although serum PTH levels have not been systematically measured.

In our opinion APD should not be administered during a predetermined period in all patients but the length of therapy should be adjusted to the changes produced upon the biochemical indexes of bone turnover. We agree with Frijlink et al [7] and Bijvoet et al [5] that a daily dose of approximately 7 mg/kg should be maintained during six months following the normalization of laboratory parameters.

Based on the presently reported studies, the following indications for the use of APD in Paget's bone disease might be suggested: 1) In the frequent cases of recent resistance to the action of EHDP or intolerance to calcitonin; 2) Patients with severe polyostotic disease and markedly elevated serum AP and urinary THP; 3) In the predominantly osteolytic lesions, due to its well known re-mineralization effect, and 4) Patients with extensive skull involvement, who usually have marked elevation of serum AP even in the absence of other skeletal localizations of Paget's disease [8] and that are frequently resistant to the effect of EHDP. On the other hand, considering the above mentioned adverse effects of APD, it is suggested that those patients with oligostotic and/or mild disease, with minor elevations of the biochemical indexes should be initially treated with EHDP. No experience has been gathered so far with the use of APD either in patients with spinal cord or brain dysfunction nor in those subjected to surgical procedures of the pagetic bones.

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Summary

Fifty seven patients with Paget's bone disease were treated with APD with an initial dose of 8.0 to 8.5 mg/kg. Eighteen patients had not been treated before whereas 39 had received previously EHDP and/or calcitonin. Clinical amelioration was observed in 77.8 % of the patients, but 12.3 % had gastric intolerance. A significant fall of both serum alkaline phosphatase and total urinary hydroxyproline was found in 78 % of the patients. The clinical and humoral response was apparently better in those patients who had not received any previous treatment but the differences were not statistically significant. Definite increments in radiological bone density were observed in five well controlled patients. It is concluded that APD should be administered preferentially in: 1) Patients not responding to EHDP or intolerant to calcitonin; 2) Patients with very severe and extensive disease; 3) Predominantly osteolytic lesions, and 4) Patients with extensive skull involvement and elevated serum alkaline phosphatase.

Resumen

EL TRATAMIENTO DE LA OSTEÍTIS DEFORMANTE DE PAGET CON UN DIFOSFONATO.

Expónese la experiencia obtenida con el tratamiento de 57 pacientes afectados de osteítis de Paget con 3-amino-1-hidroxipropilidene (APD) suministrado en dosis iniciales de 8,0-8,5 mg/kg. Dieciocho pacientes no habían sido tratados anteriormente, en tanto que 39 habían sido medicados previamente con etidronato bisódico y/o con calcitonina. Se verificó mejoría clínica en el 77,8 % y un descenso significativo de la fosfatasa alcalina suérica y de la hidroxiprolina urinaria en el 78 % de los pacientes. Las respuestas clínicas y humorales fueron aparentemente mejores en los pacientes sin tratamiento previo, aunque las diferencias no fueron estadísticamente significativas. Se destaca que hubo intolerancia gástrica en el 12,3 %, ausencia de remisión clínica y/o agravación de la sintomatología en el 22,2 % y ausencia de respuesta humoral en el 22,0 % de los casos. Se comprobó aumentos significativos de la densidad radiológica ósea en cinco casos. Se considera que la indicación del APD corresponde preferentemente en: 1) pacientes que han dejado de reaccionar al etidronato bisódico o que no toleran la calcitonina; 2) pacientes con lesiones poliostósicas y valores elevados de fosfatasa alcalina e hidroxiprolina urinaria; 3) lesiones predominantemente osteolíticas, y 4) localizaciones craneales que se acompañan de fosfatasa alcalina muy elevada.

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The adventurous physician goes on, and substitutes presumption for knowledge. From the scanty field of what is known, he launches into the boundless region of what is unknown.

El médico emprendedor procede substituyendo postulaciones con conocimientos. Así, desde el limitado campo de lo conocido, se proyecta en las ilimitadas regiones de lo desconocido.

THOMAS JEFFERSON (1743-1826)

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