

12-1983

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Recommended Citation

Mautalen, Carlos A. (1983) "Treatment of Paget's Bone Disease with the Bisphosphonate APD," *Henry Ford Hospital Medical Journal* : Vol. 31 : No. 4 , 244-248.

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Special Article

Treatment of Paget's Bone Disease with the Bisphosphonate APD†

Carlos A. Mautalen, MD*

Thirty-two patients with Paget's bone disease have been treated with the bisphosphonate APD. Nineteen had previously received treatment for Paget's disease with EHDP alone or in combination with calcitonin; 13 had not previously received treatment for Paget's disease. APD was given in a mean dose of 6.8 mg/kg of body weight during a period of 6 to 12 months. Bone pain disappeared or diminished in 91% of the patients. A very significant dim-

inution of the biochemical indices of bone turnover was observed in all patients, but the response occurred faster in patients who had not previously received treatment for Paget's disease. In 10 patients, APD therapy was discontinued after biochemical remission of the Paget's disease had been achieved. In most patients, clear signs of reactivation of the disease appeared 9 to 10 months after APD therapy was discontinued.

Several drugs, such as calcitonin (1), disodium EHDP (2-4), C_{12} MDP (5,6), or APD (7-9)† are used to treat patients with Paget's bone disease. However, none of these drugs permanently controls the disease, and in many cases the patient must be retreated when clinical symptoms recur and/or a reaction to the biochemical indices used to estimate the activity of the disease reappears.

In the present study we assessed the therapeutic efficacy of APD in the treatment of Paget's disease. We have separately evaluated patients who were previously untreated and patients whose disease had recurred following previous therapy.

Patients and Methods

We studied 32 patients with Paget's bone disease. There were 20 women and 12 men, ranging in age between 52 and 76 years (average: 65.3 years). Thirteen patients had not previously received specific treatment for Paget's bone disease, while 19 patients had previously been treated. In 10 patients the treatment consisted of EHDP alone, and in nine cases the treatment was a combination of EHDP and calcitonin. In this group of 19, an unsatisfac-

tory clinical or biochemical response to the former treatment led to the use of APD. The time interval between the suspension of the previous treatment and beginning of APD administration ranged from one to eight months with an average of 3.5 months.

The APD was given in tablets of 100 mg, half an hour before meals. The daily dose per kilogram of body weight was 4-8 mg (average: 6.8 mg). Patients who were previously untreated received APD for a minimum of six months. The treatment was prolonged when biochemical indices were not normal after six months. Previously treated patients received APD for a minimum of nine months.

Serum alkaline phosphatase was measured by the method of King and Armstrong (normal values up to 15 U/ml), and the total urinary hydroxyproline was measured by the method of Kivirikko, et al (normal values 15-40 mg/24 hrs).

Results

Clinical symptoms

Of the 32 patients, 23 had skeletal pain at the beginning of treatment. In 21 patients (91%), pain diminished or

†Note on the nomenclature: The traditional abbreviations for identifying compounds have been used in the text. According to IUPAC, Nomenclature of Organic Chemistry, Sections A-H (Oxford: Pergamon Press, 1979), the new abbreviations are as follows:

APD = AHP,BP: 3-Amino-1-hydroxypropylidene-1, 1-bisphosphonate
EHDP = HEBP: 1-Hydroxyethylidene-1, 1-bisphosphonate
 C_{12} MDP = C_{12} MBP: Dichloromethylenebisphosphonate

Submitted for publication: September 22, 1983

Accepted for publication: October 17, 1983

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Paget's Bone Disease with the Bisphosphonate APD

disappeared on APD therapy; it remained unchanged in two cases.

Although systematic radiological examination was not performed, five patients showed definite radiological improvement of bone lesions in the following sites: femur (2 cases); tibia (2 cases); and dorsolumbar spine (one patient).

Biochemical effect

The effect of APD on serum alkaline phosphatase activity is given in Table I. In patients who had not previously been treated for Paget's disease, alkaline phosphatase was significantly reduced within two months. In patients who had previously been treated, alkaline phosphatase did not drop significantly until the fourth month of therapy. The maximum decline was achieved at six months in the previously untreated patients and at 12 months in patients

who had previously been treated. The nadir in alkaline phosphatase did not significantly differ between the two groups of patients. A similar pattern was obtained with the measurement of hydroxyproline excretion (Table II).

A complete biochemical remission of the Paget's bone disease, as judged by the urine hydroxyproline excretion, was obtained in 10 of the 13 patients who had not previously been treated; the remaining three patients had a partial response. In patients who had previously been treated, seven obtained a complete remission, 11 a partial remission, and one patient failed to respond. In patients who had been previously untreated, the degree of biochemical remission was directly related to the pretreatment urine hydroxyproline excretion. In the previously treated patients, even though the basal urinary hydroxyproline of the patients with complete responses was significantly lower than that of the patients with partial responses, there was some overlap between both groups.

TABLE I
The Effect of APD on the Serum Alkaline Phosphatase in Patients with Paget's Bone Disease

	Units	Before	2 mo	4 mo	6 mo	9 mo	12 mo
		Treatment					
WPT							
Without previous treatment (13 pts)	K.A.U. %	62.1 ± 11.7 100	32.3 ± 7.7† 53.3 ± 6.0	25.5 ± 6.8† 43.6 ± 6.1	22.1 ± 5.0‡ 38.1 ± 4.2		
PT							
Previously treated (19 pts)	K.A.U. %	73.9 ± 8.5 100	70.8 ± 10.0 91.8 ± 58**	56.4 ± 8.2† 71.9 ± 5.0*	47.2 ± 6.5‡ 59.3 ± 5.4*	40.8 ± 6.4‡ 47.6 ± 4.9	31.1 ± 6.9‡ 36.7 ± 4.4

* $p < 0.01$ compared with WPT patients

** $p < 0.001$ compared with WPT patients

† $p < 0.01$ compared with the initial values (paired t test)

‡ $p < 0.001$ compared with the initial values (paired t test)

TABLE II
The Effect of APD on the Urinary Hydroxyproline Excretion in Patients with Paget's Bone Disease

	Units	Before	2 mo	4 mo	6 mo	9 mo	12 mo
		Treatment					
WPT							
Without previous treatment (13 pts)	mg/24hs %	137.4 ± 30.0 100	70.4 ± 17.4‡ 53.3 ± 5.6	58.1 ± 14.5‡ 43.4 ± 3.8	50.3 ± 13.1§ 39.0 ± 4.0		
PT							
Previously treated (19 pts)	mg/24hs %	141.8 ± 16.0 100	132.5 ± 19.1 88.0 ± 5.4**	117.2 ± 18.9† 78.0 ± 6.9**	107.4 ± 17.7‡ 70.9 ± 7.9*	98.2 ± 15.2§ 58.2 ± 4.9	83.4 ± 14.2§ 46.9 ± 3.6

* $p < 0.01$ compared with WPT patients

** $p < 0.001$ compared with WPT patients

† $p < 0.05$ compared with the initial values (paired t test)

‡ $p < 0.01$ compared with the initial values (paired t test)

§ $p < 0.001$ compared with the initial values (paired t test)

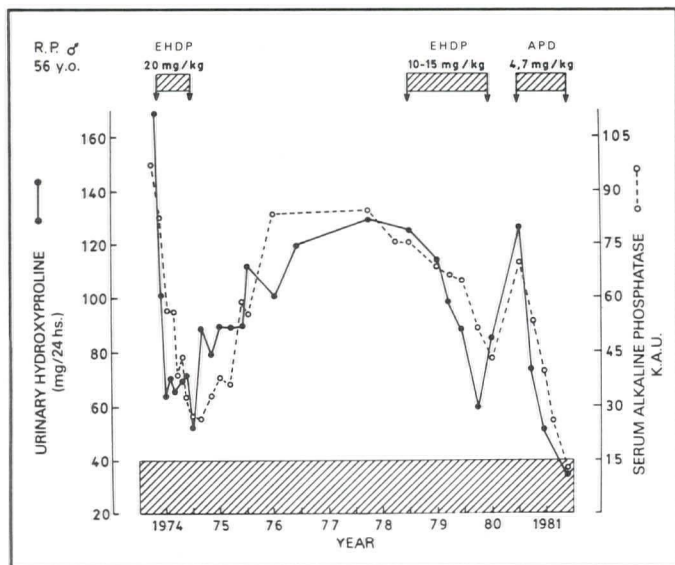


Fig. 1

Patient with Paget's bone disease of the skull. He had been treated with EHDP in the dose indicated. APD in doses of 4.7 mg/kg/day produced for the first time a biochemical remission within the normal range. (The dark zone in this figure and the following ones indicates the normal range.) The dose in mg/kg of body weight is shown above the hatched areas.

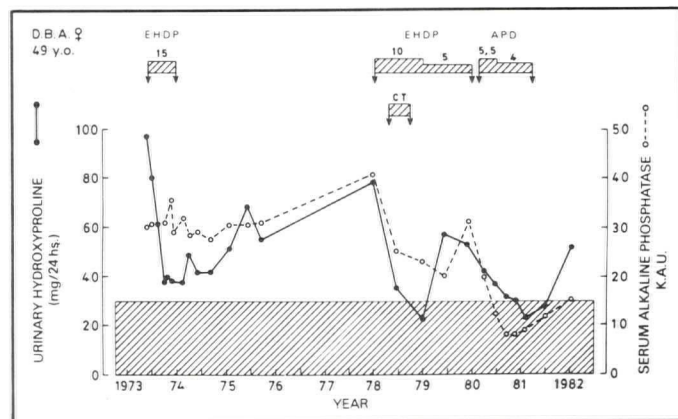


Fig. 2

Patient with Paget's disease of the left tibia. The treatment with APD decreased the serum alkaline phosphatase into the normal range, unlike former treatments. A marked radiological remineralization was observed. Nine months after suspension of APD, a significant increase of urinary hydroxyproline occurred.

Comparison of the effect of APD with previous therapy

The response to APD therapy was considered better or worse than the previous therapy when the minimum value for urinary hydroxyproline obtained during treatment with APD was at least 20% lower or higher than the minimum value observed during previous treatment. Otherwise, the response was considered "similar".

In 19 cases, the efficacy of APD was evaluated in relation to the first series of treatment with other drugs. Eleven patients had been given EHDP, seven had received EHDP combined with calcitonin, and one patient had received calcitonin only. The response was better in 47% of the cases, similar in 32%, and worse in 21%. Eleven of the 19 had received a second course of therapy before APD treatment. Six had received EHDP alone, four EHDP and calcitonin, and one calcitonin alone for the second treatment. APD was more effective in 73% of the patients and similar in the remaining 27%. The pattern of the biochemical response in four illustrative cases who had been previously treated before APD therapy is given in Figs. 1-4.

Persistence of biochemical remission

Measurements of serum alkaline phosphatase and hydroxyproline excretion were performed in 10 patients after interruption of APD treatment. The period of observation ranged between three and 15 months. The effect of APD was maintained during the first three to six months in most patients (Fig. 5). However, nine to 10 months after the suspension of treatment, clear signs of reactivation were observed in most of the examined patients.

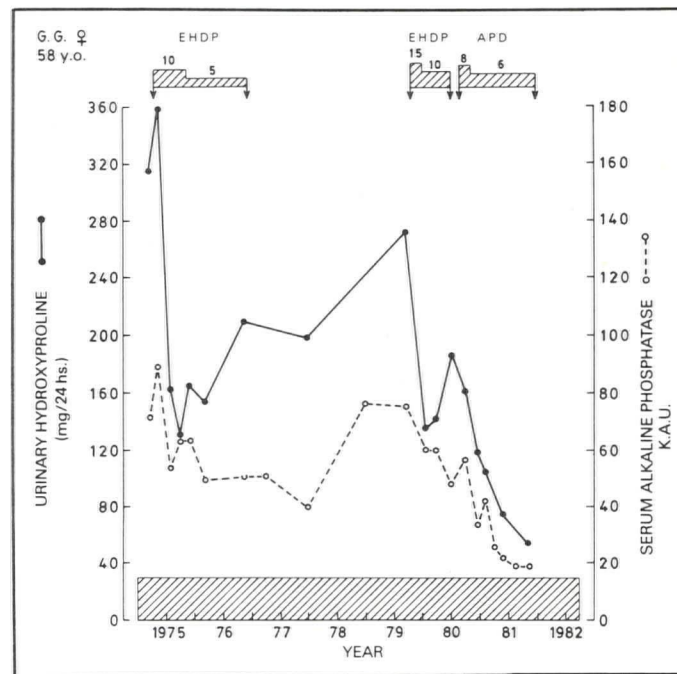


Fig. 3

Patient with polyostotic bone disease. Treatment with APD produced a greater biochemical remission than previous treatments with EHDP.

Discussion

The treatment of Paget's bone disease with APD in patients who had not previously received a specific treatment caused a satisfactory clinical and biochemical response similar to that found by other authors (7-9).

However, unlike the previous studies (7,8), the biochemical indices did not decrease into the normal range in all patients. Table III clearly shows that the ability of APD treatment to produce a decrease of the biochemical values within the normal range was related to the basal level of urinary hydroxyproline excretion. A complete remission was observed in all patients with hydroxyproline excretions lower than 150 mg/24 hrs, while in patients with excretions higher up to 200 mg/24 hrs, the decrease, while significant, did not reach normal levels. Similarly, Nagant de Deuxchaisnes (8) found that after treatment with APD, the serum alkaline phosphatase decreased to normal values in those patients whose pre-treatment levels were lower than 140IU/1, while such normalization was not attained when the basal level was higher than 200 IU/1 (normal up to 60 IU/1).

The effect of APD upon the biochemical indices was significantly slower in the patients who a few months earlier had received EHDP alone or in combination with calcitonin.

TABLE III
Relationship between Biological Response to APD and Activity of Paget's Bone Disease Judged by Urinary Hydroxyproline Excretion before Treatment

Groups		Biological Response (mg/24hrs)			
Response		Complete	Partial	Absent	
WPT Without previous treatment (13 pts)	THP	Av. ± 1SEM	82.1 ± 9.7	315.0 ± 44.8*	-
		range	(47 - 151)	(227 - 416)	
Response		7	11	1	
PT Previously treated (19 pts)	THP	Av. ± 1SEM	74.7 ± 10.4	176.4 ± 16.8*	230
		range	(53 - 126)	(78 - 257)	

* p < 0.001 compared with patients with complete biological response

Since APD occupies the same binding sites of EHDP in the hydroxyapatite crystals, it is feasible that this last compound may have initially prevented the effect of APD. However, when the administration of APD was prolonged, a satisfactory result was obtained in most patients.

Previous reports (8-11) indicated that APD has the advantage over EHDP of inducing radiological improvement in the skeletal segments affected by Paget's bone disease. In

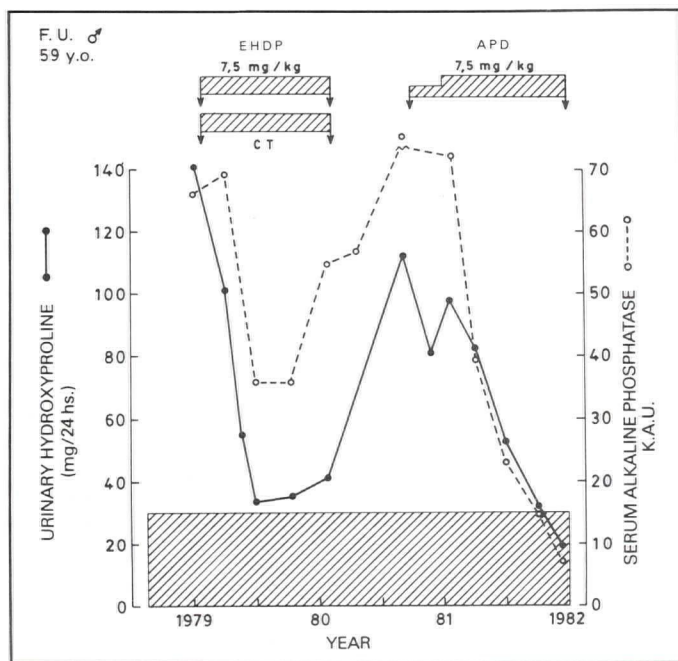


Fig. 4

Patient with Paget's bone disease of the skull, lumbar and dorsal spine, and pelvis.

The combined treatment with EHDP and calcitonin 100 IU three times a week induced a good biological effect, but the biochemical index reached the normal range during APD administration.

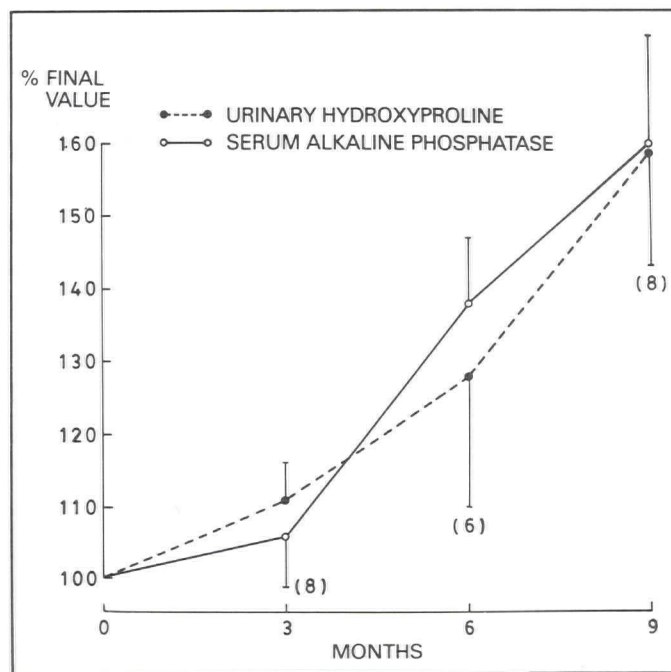


Fig. 5

Changes of the serum alkaline phosphatase and the urinary excretion of hydroxyproline after the interruption of APD administration. Values are expressed as a percentage of the final levels during APD treatment. The number of observations is indicated in parentheses.

this study marked radiological improvements in some of the treated patients were observed. In addition, it has been observed that APD caused greater biochemical remissions, compared to those induced by EHDP, except when this compound was used in a high dose, which exacerbates bone pain and significantly inhibits bone mineralization (12). Likewise, better results have been observed (13) with APD than those obtained in the same patients with the association of EHDP in an average dose of 6.5 mg/kg/day and salmon calcitonin (100 IU twice a week).

Although the number of patients observed in our study is small, the present study does not confirm former results (10) indicating that the biochemical remissions induced by APD are prolonged. Nine months after treatment suspension, a high percentage of recurrences was observed. The basal urinary hydroxyproline excretion levels suggest that the presently evaluated patients were more severely affected than those described by Frijlink, et al (7). This may

explain the faster elevation of the biochemical controls after the treatment was interrupted. Khairi, et al (2) have indicated that the severity of the disease before therapy is the most important factor influencing the postsuspension relapses after treatments with EHDP.

Calcitonin as well as compounds of the diphosphonate family have proven effective in inhibiting the accelerated bone turnover of Paget's bone disease. However, in most patients the obtained remissions are not sustained. Successive series of treatment separated by variable time intervals are required to control the disease. The present study showed that APD is an effective treatment from the clinical, radiological, and biochemical point of view, not only for patients who had not been previously treated, but also for those already treated with EHDP and/or calcitonin.

Acknowledgments

APD was supplied by Laboratorios Dr. Gador. The cooperation of Dr. Esteban Montuori is gratefully acknowledged.

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