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# From bathtub ring to osteoporosis: a clinical review of the bisphosphonates

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- **BACKGROUND** Etidronate and pamidronate are bisphosphonates, a class of chemical compounds originally used to soften hard water and prevent soap scum. Etidronate was serendipitously found to abate calcification in a child with myositis ossificans progressiva.
- **OBJECTIVE** Review the basic pharmacology of these compounds, as well as clinical uses of the approved and nonapproved forms.
- **DISCUSSION** Etidronate is approved for the treatment of hypercalcemia, Paget's disease of bone, and ectopic calcification, and has been used to treat hyperparathyroidism and nephrolithiasis with limited success. Recently it has been used to treat osteoporosis. Pamidronate is approved to treat hypercalcemia. These two drugs are the only bisphosphonates available in the United States.
- **CONCLUSIONS** Clinical trials with etidronate have aroused widespread interest in the application of bisphosphonates to treat osteoporosis. Many trials are underway to evaluate these new drugs. More information will be available within the next 5 years.

■ **INDEX TERMS:** ETIDRONATE DISODIUM; DIPHOSPHONATES; HYPERCALCEMIA; OSTEOITIS DEFORMANS; OSTEOPOROSIS; HYPERPARATHYROIDISM; KIDNEY CALCULI; MYOSITIS OSSIFICANS ■ CLEVE CLIN J MED 1993; 60:284-290

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**T**HE BISPHOSPHONATES play a significant role in the treatment of calcium and skeletal disorders: etidronate for hypercalcemia, ectopic calcification, and Paget's disease of bone, and pamidronate for hypercalcemia. The greatest attention is now focused on the use of these drugs to treat osteoporosis. Clinical trials with etidronate have aroused widespread interest in the application of bisphosphonates to treat this common and costly disorder. In this review, I discuss the basic pharmacology of these compounds and use etidronate as the model for most of the discussion. I then discuss some of the clinical uses of the approved and nonapproved forms. Extensive reviews of the topic can be found elsewhere.<sup>1,2</sup>

## INTRODUCTION

Etidronate and pamidronate are the only bisphosphonate drugs marketed in the United States. These are a class of chemical compounds that were originally developed for the commercial sector as detergent additives to soften hard water and to prevent soap

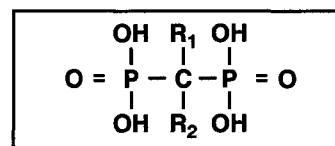
scum.<sup>3,4</sup> It was serendipitous that the original compound, etidronate, was used in a clinical setting many years ago. The first patient was a child with the life-threatening disease myositis ossificans progressiva that was slowly impairing the respiratory musculature because of ectopic calcification.<sup>1,3</sup> After treatment with etidronate, the calcification process abated and muscle function became normal. Since then, etidronate has been studied in a variety of calcium disorders and finally approved for the treatment of hypercalcemia, Paget's disease of bone, and ectopic calcification. It has also been used to treat hyperparathyroidism and nephrolithiasis with limited success, and recently it has been used to treat osteoporosis. Pamidronate is approved to treat hypercalcemia. Although only these two drugs are available in the United States, many other analogs are under study worldwide (Figure).

#### CHEMISTRY

The bisphosphonates are synthetic analogs of pyrophosphate (Figure). Like pyrophosphate, they have a high affinity for calcium phosphate crystal (hydroxyapatite) of bone. A central carbon atom of the bisphosphonate substitutes for the oxygen atom of pyrophosphate. This minor change prevents rapid hydrolysis of the drug by endogenous pyrophosphatase and thereby prolongs the pharmacological activity. Substituents on this carbon atom produce the unique compounds. The  $R_1$  groups (Figure) control the affinity of the molecule for hydroxyapatite, whereas the  $R_2$  groups impart most of the pharmacological activity but can also affect adsorption to bone due to steric considerations.<sup>1,3,4</sup>

#### PHARMACOLOGY

These drugs alter the rate of bone turnover. It was originally thought that this activity arose from the high affinity of the chemical compound for bone mineral.<sup>5</sup> It soon became apparent, however, that the amount of drug adsorbed in vivo was too small to accomplish this by mere adsorption to mineral binding sites. It is now accepted that alterations in the number and activity of osteoclasts, or their precursors, account for the pharmacological activity. A variety of effects are noted on cellular biochemistry (Table 1). Stimulation and inhibition of critical cell functions is seen when the drugs are studied in vitro. Contradictory effects arise from differences in the in





	$R_1$	$R_2$
<b>Etidronate</b>	- OH	- CH <sub>3</sub>
<b>Clodronate</b>	- Cl	- Cl
<b>Pamidronate</b>	- OH	- (CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub>
<b>Alendronate</b>	- OH	- (CH <sub>2</sub> ) <sub>3</sub> NH <sub>2</sub>
<b>Risedronate</b>	- OH	- CH <sub>2</sub> 
<b>Tiludronate</b>	- H	- S 

FIGURE. Chemical structures of the clinical bisphosphonates.

vitro models, the doses used, and the idiosyncrasies of the individual bisphosphonates.

Physicochemical interaction between these compounds and hydroxyapatite crystal was the original explanation for their inhibition of bone resorption.<sup>5</sup> In vivo, data have necessitated a reevaluation and forced consideration of other explanations of activity. Most studies concentrate on impairment of osteoclast function. Some studies emphasize effects on immature precursors of osteoclasts, since these require less drug to impair activity than the adult cell.<sup>6</sup> In tissue culture, bisphosphonates impair resorption cavities in bone by altering the cytoskeleton of osteoclasts and inhibiting changes in osteoclastic cell membrane required for bone resorption.<sup>7,8</sup> Experiments with etidronate and clodronate show an inhibition of osteoclastic development from hematopoietic precursors.<sup>9</sup> On the other hand, pamidronate impairs in vitro bone formation.<sup>10</sup>

New avenues of investigation indicate that these drugs may alter intracellular biochemical messengers. There is an emerging interest in the role these drugs play in the production of macrophage cytokines that control skeletal function. One important regulator is interleukin-1. This protein stimulates bone turnover and connective tissue metabolism, in addition to other actions.<sup>1,11</sup> Some studies, but not all, show that bisphosphonates impair the production of interleukin-1 by macrophages.<sup>12,13</sup>

**TABLE 1**  
CELLULAR EFFECTS OF BISPHOSPHONATES\*

Cellular activity	Bisphosphonate effects <sup>†</sup>
Glycogen synthesis	+
Fatty acid oxidation	+
Cartilage synthesis	+
Alkaline phosphatase production	+ -
Cell replication	+ -
Lactic acid production	+ -
Proteoglycan synthesis	+ -
Mitochondrial release of calcium	+ -
Interleukin-1 effect	-
Lysosomal enzymes	-
Prostaglandin synthesis	-
Cyclic adenosine monophosphate production	+ -

\*Adapted from reference 4

<sup>†</sup>+, stimulated; -, inhibited

In summary, no single explanation fully describes the mechanism of action of these drugs *in vivo*. Contradictory results occur because each drug has unique actions in different experimental systems.

#### HUMAN PHARMACOLOGY

A consistent finding with all bisphosphonates is their poor absorption from the gastrointestinal tract. Under optimal conditions, the average absorption of pamidronate, etidronate, and clodronate is 0.2% to 1.0% in the rat, 1% to 9% in the dog, and 1% to 2% in humans.<sup>1,2,14</sup> The presence of food or calcium in the intestine further impairs absorption. The circulating half-life is short because skeletal uptake is rapid.<sup>1</sup> Urinary excretion ranges from one third to one half of an absorbed dose.<sup>1</sup> Retention in the skeleton is very long.

Effects on serum calcium and phosphorus occur as well. Some of these drugs can cause hypocalcemia, but the magnitude is a function of the individual drug. This effect is exploited to treat malignant hypercalcemia (see below). The drugs enhance renal tubular reabsorption of phosphorus and secondarily increase serum phosphorus.<sup>15</sup> The duration and magnitude of this effect vary with the degree of secondary hyperparathyroidism generated by the individual drug.<sup>15</sup>

The long residence time of bisphosphonates in bone is a concern, since prolonged inhibition of osteoclast function eventually turns off bone formation and causes a mineralization defect (ie, osteomalacia). This effect is seen in the treatment of

Paget's disease with etidronate if the dose and duration are excessive. Daily doses of 20 mg/kg body weight for only 4 weeks induce a mineralization defect that persists up to 10 weeks after discontinuing the drug.<sup>16</sup> Uninterrupted use for 18 to 30 months causes fractures in normal bone.<sup>17</sup> Lower doses of 5 to 8 mg/kg body weight daily for 6 months cause scattered areas of osteomalacia.<sup>18</sup> Partial amelioration of this effect occurs with the concomitant use of analogs of vitamin D.<sup>19</sup> In experimental studies in dogs, parenteral administration of etidronate in doses of 2 mg/kg body weight inhibits mineralization of tissue ingrowth into cementless skeletal prostheses.<sup>20</sup> This inhibition of skeletal growth formation is of much greater concern with etidronate than with the second-generation bisphosphonates. For example, pamidronate causes a 50% reduction in bone mineral growth at a dose that is 50 times greater than the one used to inhibit bone resorption.<sup>2</sup> Thus, the second-generation bisphosphonates are less likely to impair bone mineralization at therapeutic doses.

#### MEDICAL THERAPY

Both pamidronate and etidronate are approved to treat hypercalcemia. Etidronate is also approved to treat Paget's disease of bone. The nonapproved uses of bisphosphonates are extensive. The most promising application of these agents is to treat osteoporosis. The following sections cover the application of these drugs in the treatment of hyperparathyroidism, nephrolithiasis, ectopic calcification, and osteoporosis as well as Paget's disease of bone and hypercalcemia.

#### Paget's disease of bone

Paget's disease is the most common problem for which the bisphosphonates are used. Almost all the agents listed have been used to treat Paget's disease in a variety of clinical studies around the world. Etidronate was originally prescribed in oral doses from 5 to 20 mg/kg body weight daily for a 6-month period alternating with a 6-month drug-free period.<sup>21-23</sup> Up to 60% of patients respond to this treatment. Forty percent have a prolonged response to a single treatment cycle. About 15% may be resistant. Resistant patients require maximal doses of drugs. Characteristically, these patients have serum alkaline phosphatase levels six times normal and urinary hydroxyproline levels 10 times normal.

Doses greater than 10 mg/kg body weight daily impair bone mineralization and cause fractures and bone pain.<sup>23</sup> The other bisphosphonates have also been studied in this disorder. A total dose of 50 mg of alendronate given as five daily infusions suppresses serum alkaline phosphatase 75% and urinary hydroxyproline 45% within 4 weeks of the initial dose and maintains a serum alkaline phosphatase level of about 50% of pretreatment values for up to 6 months.<sup>24</sup> Oral doses of pamidronate (500 mg daily) for 4 to 12 months and intravenous doses (20 mg daily) for 10 days produce clinical remission in about 91% of patients.<sup>25,26</sup> A single intravenous dose of 60 mg has sustained effects on disease activity for about a year, and lower doses of 15 to 45 mg daily induce varying degrees of remission.<sup>26,27</sup> Pamidronate may be useful to treat cases of Paget's disease resistant to other therapies.<sup>28</sup> Clodronate also shows efficacy in controlling the disease at oral doses of 1600 mg daily.<sup>29</sup>

### Hyperparathyroidism

Since these drugs impair bone resorption and skeletal turnover, it was logical to investigate their efficacy in treatment of hypercalcemia caused by hyperparathyroidism. The results, however, have been disappointing.

Etidronate and clodronate decrease urinary hydroxyproline and calcium in hyperparathyroid patients, but the drugs don't affect serum calcium or parathyroid hormone secretion.<sup>29,30</sup> The lack of effect on serum calcium implied that renal tubular reabsorption of calcium promoted by parathyroid hormone was the major cause of hypercalcemia and not skeletal resorption. Bisphosphonates do not affect renal tubular handling of calcium and therefore would have little effect on the serum calcium level in this circumstance. Although not proven, it is a rational expectation that these agents might control skeletal pain in cases where bone pain may exist.

### Hypercalcemia

All bisphosphonates are theoretically capable of controlling acute hypercalcemia caused by malignancy, since this disorder generally arises from rapid skeletal destruction. However, there may be a component of hypercalcemia related to renal tubular reabsorption for which bisphosphonates are not effective.<sup>31</sup> Intravenous infusions of etidronate for 1 to 4 days at a dose of 7.5 mg/kg body weight control hypercalcemia within a week of administration.

Response rates are 63% to 73%.<sup>32,33</sup> A single 60-mg dose of pamidronate achieves a similar effect.<sup>34</sup> Oral and intravenous doses of clodronate have also been used.<sup>29,35</sup> Clodronate and etidronate produce normocalcemia within 10 days. Clodronate produced a more rapid rate of fall in serum calcium at 3 days than etidronate.<sup>35</sup> A study comparing pamidronate and etidronate showed similar reductions in serum calcium, but a larger number of patients responded to pamidronate (70%) than to etidronate (41%).<sup>36</sup> Some studies, but not all, indicate that oral etidronate can maintain normocalcemia after the acute hypercalcemia is controlled.<sup>37-39</sup>

### Nephrolithiasis

Bisphosphonates inhibit the *in vitro* crystallization of calcium phosphate and calcium hexalate, constituents of renal stones.<sup>40,41</sup> Daily etidronate doses of 5 to 20 mg/kg body weight inhibit calcium phosphate crystalluria in patients.<sup>42</sup> Other studies show that administration of etidronate decreases the size of urinary calcium oxalate crystals but increases the total urinary concentration of oxalate.<sup>43</sup> Placebo-controlled studies show a decrease in stone events from 2.4 to 0.2 per year.<sup>44</sup> Doses of 10 to 20 mg/kg body weight were used for 1 to 12 months. Abnormalities in skeletal mineralization were noted in a study.<sup>45</sup> This adverse effect limits the use of etidronate in the treatment of stone disease. There are no data regarding the efficacy or side effects of the other bisphosphonates.

### Ectopic calcification

Myositis ossificans progressiva is a rare, dominantly inherited disorder which involves skeletal malformation, calcification of muscle, tendons, connective tissue, ligaments, and joint capsules.<sup>46,47</sup> Ectopic calcification may arise spontaneously or from traumatic events. Etidronate has been used in a limited number of patients with this problem, but these observations are from anecdotal, uncontrolled studies.<sup>48-50</sup> Generally, a large dose is employed (ie, up to 20 mg/kg body weight daily) but evidence of mineralization defect is seen.<sup>51,52</sup> This finding limits the use of etidronate. The second-generation drugs may be less toxic to bone, but this would involve another mechanism which has not been elaborated.

### Osteoporosis

Treating osteoporosis is the latest therapeutic application of the bisphosphonates. Two major studies,



**TABLE 2**  
EFFECT OF BISPHOSPHONATES ON SPINAL BONE MINERAL DENSITY (BMD)  
IN POSTMENOPAUSAL OSTEOPOROTIC WOMEN

Reference	Drug	Patients enrolled in study	Study design	Treatment duration (years)	Percent change in BMD at end of study	Percent change in BMD per year
53	Etidronate	66	Placebo-controlled, blinded, randomized, two groups	2.8	5.3 (at end of study n = 20)	1.9
54	Etidronate	423	Placebo-controlled, randomized, blinded, four groups	2	4.2 to 5.2	2.1 to 2.6
55	Pamidronate	24	Not randomized, no controls	1.4 to 6.2	6.8 ± 1.7	3.0
58	Pamidronate	35	Not randomized, not blinded, no controls	1.5	7.5 ± 1.4	5.0
59	Pamidronate	18	Not randomized, not blinded, no controls	3 to 5	2.4 (at end of 2 years)	1.2
60	Etidronate	47	Not blinded, not randomized	2	15.7 ± 1.7	7.8

one in Europe and the other in the United States, have shown a beneficial effect of etidronate in the treatment of osteoporosis.<sup>53,54</sup> In the European protocol, etidronate was given for 14 days every 15 weeks.<sup>53</sup> In the United States protocol, etidronate was given with or without a stimulator of bone metabolism.<sup>54</sup> Etidronate was superior to placebo in decreasing fractures<sup>53</sup> and increasing bone density.<sup>53,54</sup>

A number of scientific concerns about these studies have been expressed, but the greatest concern from a clinical point of view is the long-term effect of the drug on bone formation and fracture rate. However, bone biopsy studies of patients treated with cyclic etidronate for 5 to 7 years showed no significant effect of the drug on bone formation.<sup>56</sup> Pharmacokinetic studies show that the amount of etidronate that is theoretically retained in the skeleton of human subjects or experimental animals with this cyclical therapy would be distributed to a small fraction of the active remodeling surface of the bone and, therefore, would not totally suppress bone formation.<sup>57</sup>

A comparison of the effects of several bisphosphonates on mineral density of osteoporotic patients is noted in Table 2. Increased mineral density is achieved with all bisphosphonates studied. The increases range from 1.2% to 7.8% per year. Study designs are variable. The number of par-

ticipants in each study, except for one protocol, is small. Not all studies assess fracture reduction, which makes it difficult to compare efficacy.

Another use of these agents is to *prevent* osteoporosis. Experimental studies with alendronate, etidronate, and risedronate show suppression of bone loss in ovariectomized animals.<sup>61-63</sup> Alendronate was used every 2 weeks for a year and risedronate was used for 1 of every 4 weeks for about a year.

In postmenopausal women, tiludronate prevents bone loss. A 6-month, double-blinded, randomized trial with 100 mg per day preserves skeletal lumbar mass. This effect persisted for an additional 6 months after treatment was stopped.<sup>64</sup> Women treated for arteritis with prednisone had no spinal bone loss when given cyclical etidronate concurrently with the steroid.<sup>65</sup> Pamidronate (150 mg daily) and calcium (1 g daily) prevented steroid-induced cortical bone loss.<sup>66</sup> Hence, these drugs may well become ancillary therapy in the long-term use of glucocorticoids.

#### ADVERSE EFFECTS

It is difficult to make a generic statement about the toxicity of this drug class because the uniqueness of each compound brings forth idiosyncratic side effects.<sup>67</sup> Etidronate has been generally well

tolerated. The major complaints have been gastrointestinal—dyspepsia, diarrhea, bloating, and spasm. Renal dysfunction is a concern when these drugs are given intravenously for the treatment of hypercalcemia. Administration over 2 or more hours avoids this concern. Efficacy is not a function of the duration of administration. For example, pamidronate is equally effective whether given over 2 or 24 hours.<sup>68</sup> The long-term use of etidronate causes mineralization defects (see sections on pharmacology and therapy). The second-generation agents do not lead to this problem because the therapeutic doses used to treat high bone turnover are much smaller than the doses causing mineralization changes. A peculiar side effect is hyperpyrexia. It develops only after the first dose of one of the amino- $R_2$ -group compounds and disappears with subsequent usage. The release of mononuclear cytokines may account for this.<sup>67</sup>

## SUMMARY

The bisphosphonates enjoy a significant place in the treatment of calcium and skeletal disorders. Use of etidronate in the management of hypercalcemia, ectopic calcification, and Paget's disease of bone is well established. Pamidronate is approved to treat hypercalcemia and undoubtedly will be evaluated and approved to treat Paget's disease. The greatest attention is now focused on the use of these drugs to treat osteoporosis. The clinical trials with etidronate are a historical milestone in the field of osteoporosis. They have aroused widespread interest in the application of bisphosphonates to treat this common and costly disorder. The etidronate trials are a model for all studies with the second-generation agents. Accordingly, many trials are underway to evaluate these new drugs. More information will be available within the next 5 years.

## REFERENCES

1. Fleisch H. Bisphosphonates: a new class of drugs in diseases of bone and calcium metabolism. *Recent Results Cancer Res* 1989; 116:1–27.
2. Fitton A, McTavish D. Pamidronate—a review of its pharmacological properties and therapeutic efficacy in resorptive bone disease. *Drugs* 1991; 41:289–318.
3. Francis MD, Centner RL. The development of diphosphonates as significant health care product. *J Chem Educ* 1978; 55:760–766.
4. Francis MD. A brief history of etidronate. In: Summit L, editor. *Diphosphonates: the first decade. A symposium on diphosphonates in the management of metabolic bone disease*. Williamsburg, Virginia: Virginia Commonwealth University, 1988:7–14.
5. Fleisch H, Russell RGG, Francis MD. Diphosphonates inhibit hydroxyapatite dissolution *in vitro* and bone resorption in tissue culture and *in vivo*. *Science* 1969; 165:1262–1264.
6. Boonekamp PM, van der Wee-Pals LJA, van Wijk-van Lennep MML, Thesing C, Bijvoet OLM. Two modes of action of bisphosphonates on osteoclastic resorption of mineralized matrix. *Bone Miner* 1986; 1:27–39.
7. Sato M, Grasser W. Effects of bisphosphonates on isolated rat osteoclasts as examined by reflected light microscopy. *J Bone Miner Res* 1990; 5:31–40.
8. Sato M, Grasser W, Endo N, et al. Bisphosphonate action—alendronate localization in rat bone and effects on osteoclast ultrastructure. *J Clin Invest* 1991; 88:2095–2105.
9. Hughes DE, MacDonald BR, Russell RGG, Gowen M. Inhibition of osteoclast-like cell formation by bisphosphonates in long-term cultures of human bone marrow. *J Clin Invest* 1989; 83:1930–1935.
10. Marie PG, Hott M, Garba M-T. Inhibition of bone matrix apposition by (3-amino-1-hydroxypropylidene)-1,1-bisphosphonate (AHPBP) in the mouse. *Bone* 1985; 6:193–200.
11. Centrella M, Canalis E. Local regulators of skeletal growth: a perspective. *Endocr Rev* 1985; 6:544–551.
12. Aida Y, Toda Y, Shimakoshi Y, Yamada K, Aono M. Effects of disodium ethane-1-hydroxy-1,1-diphosphonate (EHDP) on interleukin-1 production by macrophages. *Microbiol Immunol* 1986; 30:1199–1206.
13. Evequoz V, Trechsel U, Fleisch H. Effect of bisphosphonates on production of interleukin 1-like activity by macrophages and its effect on rabbit chondrocytes. *Bone* 1985; 6:439–444.
14. Fogelman I, Smith L, Mazess R, Wilson MA, Bevan JA. Absorption of oral diphosphonate in normal subjects. *Clin Endocrinol (Oxf)* 1986; 24:57–62.
15. McCloskey EV, Yates AJ, Gray RES, Hamdy NAT, Galloway J, Kanis JA. Diphosphonates and phosphate homeostasis in man. *Clin Sci* 1988; 74:607–612.
16. Gibbs CJ, Aaron JE, Peacock M. Osteomalacia in Paget's disease treated with short term, high dose sodium etidronate. *Br Med J* 1986; 292:1227–1229.
17. Mautalen C, Gonzalez D, Blumenfeld EL, Aravjo ES, Schajowicz F. Spontaneous fractures of uninvolved bones in patients with Paget's disease during unduly prolonged treatment with disodium etidronate (EHDP). *Clin Orthop* 1986; 207:150–155.
18. Boyce BF, Fogelman I, Ralston S, et al. Focal osteomalacia due to low-dose diphosphonate therapy in Paget's disease. *Lancet* 1984; 1:821–824.
19. Ralston SH, Boyce BF, Cowan RA, et al. The effect of 1-alpha-hydroxyvitamin D (3) on the mineralization defect in sodium etidronate-treated Paget's disease—a double-blind randomized clinical study. *J Bone Miner Res* 1987; 2:5–12.
20. Rivero DP, Skipor AK, Singh M, Urban R, Galante JO. Effect of disodium etidronate (EHDP) on bony ingrowth in a porous material. *Clin Orthop* 1987; 215:279–286.
21. Siris ES, Canfield RE, Jacobs TP, Stoddart KE, Spector PJ. Clinical and biochemical effects of EHDP in Paget's disease of bone: patterns of response to initial treatment and to long-term therapy. *Metab Bone Dis Relat Res* 1981; 3:301–308.
22. Altman RD. Long-term follow-up of therapy with intermittent etidronate disodium in Paget's disease of bone. *Am J Med* 1985; 1979:583–590.
23. Krane SM. Etidronate disodium in the treatment of Paget's disease of bone. *Ann Intern Med* 1982; 96:619–625.
24. O'Doherty DP, Gertz BJ, Tindale W, et al. Effects of five daily 1 hr infusions of alendronate in Paget's disease of bone. *J Bone Miner Res* 1992; 7:81–87.
25. Harinck HJ, Papapoulos SE, Blanksma HJ, et al. Paget's disease of bone: early and late responses to three different modes of

- treatment with aminohydroxypropylidene bisphosphonate (APD). *Br Med J* 1987; 295:1301-1305.
26. Mautalen CA, Gonzalez D, Ghiringhelli G. Efficacy of the bisphosphonate APD in the control of Paget's disease. *Bone* 1985; 6:429-432.
  27. Thiebaud D, Jaeger P, Gobelet C, Jacquet AF, Burckhardt P. A single infusion of bisphosphonate AHPBP (APD) as treatment of Paget's disease of bone. *Am J Med* 1988; 1985:207-212.
  28. Mallette LE. Successful treatment of resistant Paget's disease of bone with pamidronate. *Arch Intern Med* 1989; 149:2765-2767.
  29. Douglas DL, Russell RCG, Preston CJ, et al. Effect of dichloromethylene diphosphonate in Paget's disease of bone and in hypercalcemia due to hyperparathyroidism or malignant disease. *Lancet* 1980; 1:1043-1047.
  30. Kaplan RA, Geho WB, Poindexter C, et al. Metabolic effects of diphosphonate in primary hyperparathyroidism. *J Clin Pharmacol* 1977; 17:410-419.
  31. Thiebaud D, Jaeger P, Burckhardt P. Response to retreatment of malignant hypercalcemia with the bisphosphonate AHPBP (APD): respective role of kidney and bone. *J Bone Miner Res* 1990; 5:221-226.
  32. Ryzen E, Martodam RR, Troxell M, et al. Intravenous etidronate in the management of malignant hypercalcemia. *Arch Intern Med* 1985; 145:449-452.
  33. Singer FR, Ritch PS, Lad TE, et al. Treatment of hypercalcemia in malignancy with intravenous etidronate—a controlled multicenter study. *Arch Intern Med* 1991; 151:471-476.
  34. Thiebaud D, Jaeger P, Jacquet AF, Burckhardt P. A single-day treatment of tumor-induced hypercalcemia by intravenous aminohydroxypropylidene bisphosphonate. *J Bone Miner Res* 1986; 1:555-562.
  35. Jung A. Comparison of two parenteral diphosphonates in hypercalcemia malignancy. *Am J Med* 1982; 72:221-226.
  36. Gucalp R, Ritch P, Wiernik PH, et al. A comparative study of pamidronate disodium and etidronate disodium in the treatment of cancer-related hypercalcemia. *J Clin Oncol* 1992; 10:134-142.
  37. Meunier PJ, Chapuy MC, Delmas P, et al. Intravenous disodium etidronate therapy in Paget's disease of bone and hypercalcemia of malignancy. Effects on biochemical parameters and bone histomorphometry. *Am J Med* 1987; 82:71-78.
  38. Ringenberg QS, Ritch PS. Efficacy of oral administration of etidronate disodium in maintaining normal serum calcium levels in previously hypercalcemic cancer patients. *Clinical Ther* 1987; 9:318-324.
  39. Schiller SH, Rasmussen R, Benson A, et al. Maintenance etidronate in the prevention of malignancy-associated hypercalcemia. *Arch Intern Med* 1987; 147:963-966.
  40. Ohata M, Pak CYC. The effect of diphosphonate on calcium phosphate crystallization in urine *in vitro*. *Kidney Int* 1973; 4:401-406.
  41. Pak CYC, Ohata M, Holt K. Effect of diphosphonate on crystallization of calcium oxalate *in vitro*. *Kidney Int* 1975; 7:154-160.
  42. Ohata M, Pak CYC. Preliminary study in the treatment of nephrolithiasis (calcium stones) with diphosphonate. *Metabolism* 1974; 23:1167-1173.
  43. Robertson WG, Peacock M, Marshall RW, Knowles F. The effect of ethane-1-hydroxy-1,1-diphosphonate (EHDP) on calcium oxalate crystalluria in recurrent renal stone-formers. *Clin Sci Mol Med* 1974; 47:13-22.
  44. Bauman M, Bisaz S, Fleisch H, Wacker M. Biochemical and clinical effects of ethane-1-hydroxy-1,1-diphosphonate in calcium nephrolithiasis. *Clin Sci Mol Med* 1978; 54:509-516.
  45. McCredie PA, Paul HR, Rotenberg E. Diphosphonate therapy in nephrocalcinosis. *Br J Urol* 1976; 48:93-100.
  46. Connor JM, Evans DAP. Fibrodysplasia ossificans progressiva: the clinical features and natural history of 34 patients. *J Bone Joint Surg* 1982; 64-B:76-83.
  47. Rogers JG, Geho WB. Fibrodysplasia ossificans progressiva—a survey of forty-two cases. *J Bone Joint Surg* 1979; 61-A:909-914.
  48. Hentzer B, Jacobson HH, Asboe-Hansen G. Fibrodysplasia (myositis) ossificans progressiva treated with disodium etidronate. *Radiology* 1978; 29:69-75.
  49. Holmsen H, Ljunghall S, Hierton T. Myositis ossificans progressiva—clinical and metabolic observations in a case treated with a diphosphonate (EHDP) and surgical removal of ectopic bone. *Acta Orthop Scand* 1979; 50:33-38.
  50. Rogers JG, Dorst JP, Geho WB. Use and complications of high dose disodium etidronate therapy in fibrodysplasia ossificans progressiva. *J Pediatr* 1977; 91:1011-1014.
  51. Weinstein RS. Focal mineralization defect during disodium etidronate treatment of calcinosis. *Calcif Tissue Int* 1982; 34:224-228.
  52. Nolen AJG. Effects of ethylhydroxydiphosphonate (EHDP) on heterotopic ossification. *Acta Orthop Scand* 1986; 57:358-361.
  53. Storm T, Thamsborg G, Steiniche T, Genant HK, Sorensen OH. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. *N Engl J Med* 1990; 322:1265-1271.
  54. Watts NB, Harris ST, Genant HK, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. *N Engl J Med* 1990; 323:73-79.
  55. Valkema P, Vismans FJFE, Papapoulos SE, Pauwels EKJ, Bijvoet OLM. Maintained improvement in calcium balance and bone mineral content in patients with osteoporosis treated with bisphosphonate (APD). *Bone Miner* 1989; 5:183-192.
  56. Steiniche S, Thamsborg G, Sorensen O, Nelson F. Histomorphometric evaluation of trabecular bone in osteoporotic patients on long term etidronate treatment [abstract]. *J Bone Miner Res* 1992; 7 Suppl 1:330.
  57. Kasting GB, Francis MD. Retention of etidronate in human, dog and rat. *J Bone Miner Res* 1992; 7:513-522.
  58. Fromm GA, Vega E, Plantalech L, Galich AM, Mautalen CA. Differential action of pamidronate on trabecular and cortical bone in women with involutional osteoporosis. *Osteoporosis International* 1991; 1:129-133.
  59. DeVogelaar JP, de Deuschaines N. Treatment of involutional osteoporosis with the bisphosphonate APD (disodium pamidronate); non-linear increase of lumbar bone mineral density [abstract]. *J Bone Miner Res* 1990; 5 Suppl 2:251.
  60. Miller PD, Neal BJ, McIntyre DO, Yanover MJ, Anger MS, Kowalski L. Effect of cyclical therapy with phosphorus and etidronate on axial bone mineral density in postmenopausal osteoporotic women. *Osteoporosis International* 1991; 1:171-176.
  61. Wronski TJ, Yen CF, Scott KS. Estrogen and diphosphonate treatment provide long-term protection against osteopenia in ovariectomized rats. *J Bone Miner Res* 1991; 6:387-394.
  62. Seedor JG, Quartuccio HA, Thompson DD. The bisphosphonate alendronate (MK-217) inhibits bone loss due to ovariectomy in rats. *J Bone Miner Res* 1991; 6:339-346.
  63. Thompson DD, Seedor JG, Quartuccio H, et al. The bisphosphonate, alendronate, prevents bone loss in ovariectomized baboons. *J Bone Miner Res* 1992; 7:951-960.
  64. Reginster JY, Deroisy R, Denis D, et al. Prevention of postmenopausal bone loss by tiludronate. *Lancet* 1989; 2:1469-1471.
  65. Mulder H, Sneider HAA. Effect of cyclical etidronate regimen on prophylaxis of bone loss of glucocorticoid (prednisone) therapy in post menopausal women [abstract]. *J Bone Miner Res* 1992; 7 Supplement 1:331.
  66. Reid IR, Alexander CJ, King AR, Ibbertson HK. Prevention of steroid induced osteoporosis with (3-amino-1-hydroxypropylidene)-1,1 bisphosphonate (APD). *Lancet* 1988; 1:143-145.
  67. Fleisch H. Bisphosphonates—pharmacology and use in the treatment of tumor-induced hypercalcemic and metastatic bone disease. *Drugs* 1991; 42:919-939.
  68. Dodwell DJ, Howell A, Morton AR, Daley-Yates PT, Hoggarth CR. Infusion rate and pharmacokinetics of intravenous pamidronate in the treatment of tumor-induced hypercalcemia. *Postgrad Med J* 1992; 68:434-439.