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Publication Date
2020-05-01

DOI
10.1016/j.bone.2020.115222

Peer reviewed

Bone 134 (2020) 115222

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Full Length Article

History of etidronate

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ARTICLE INFO

Keywords:
Bisphosphonates
Etidronate
Paget's disease
Osteoporosis
Fracture

ABSTRACT

Etidronate is a non-nitrogen-containing bisphosphonate. Because it binds with calcium and inhibits crystal formation and dissolution, it was considered by Procter & Gamble as an additive to toothpaste (to prevent build-up of tartar) and detergent (to bind calcium and increase sudsing in "hard" water). The first clinical use (1968) was for fibrodysplasia ossificans progressiva. The first approved clinical use (1977) was for treatment of Paget's disease of bone. Other approved indications are hypercalcemia of malignancy and heterotopic ossification, with a host of off-label uses (including fibrous dysplasia, periodontal disease, multiple myeloma, neuropathic arthropathy, pulmonary microlithiasis, diabetic retinopathy, bone metastases, melorheostosis, urinary stone disease, periodontal disease, etc.). Unique among bisphosphonates, etidronate (oral therapy) results in hyperphosphatemia, increased tubular reabsorption of phosphorus and increased levels of 1,25-dihydroxyvitamin D. The dose that reduces bone resorption is close to the dose that impairs mineralization; prolonged high-dose use can result in osteomalacia and bone fractures. Intermittent cyclic etidronate for osteoporosis resulted in favorable changes in bone density and histomorphometry (no mineralization defect) as well as a decrease in vertebral fracture rates in postmenopausal women with osteoporosis. Later studies showed similar effects in men with osteoporosis and patients with glucocorticoid-induced osteoporosis. Although its use for osteoporosis has given way to newer bisphosphonates and other agents, because of its unique properties, it remains the bisphosphonate of choice for treatment of heterotopic ossification.

1. Introduction

Etidronate (disodium ethane-1-hytdroxy-1,1-bisphosphonate) is a non-nitrogen-containing bisphosphonate – two phosphonate groups bound to a carbon [Fig. 1] – was first synthesized in 1897. Because it binds with calcium and inhibits crystal formation and dissolution, Procter & Gamble considered it as an additive to toothpaste (to prevent build-up of tartar) [1] and detergent (to bind calcium and increase sudsing in "hard" water) [2]. Subsequent references need to be renumbered.

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https://doi.org/10.1016/j.bone.2020.115222
Received 3 December 2019; Received in revised form 19 December 2019; Accepted 2 January 2020
Available online 03 January 2020
8756-3282/

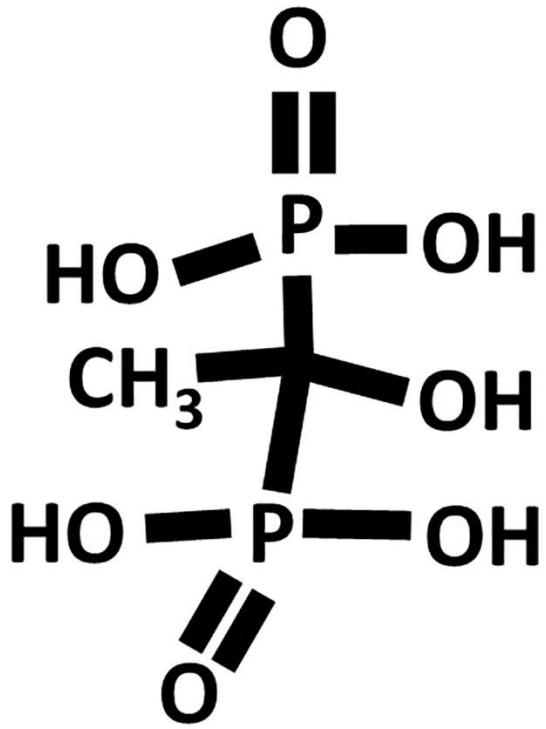

Fig. 1. Chemical structure of etidronate.
Modified from R.G.G. Russell, N.B. Watts, F.H. Ebetino, M.J. Rogers, Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy, Osteoporos Int. 19 (2008) 733–759, used with permission.

Preclinical studies showed potential therapeutic effects. In addition to inhibiting crystal formation and dissolution [3], reduced osteoclast activity and increased bone volume were observed [4].

Given the common use of nitrogen containing bisphosphonates today, some of the unique properties of etidronate may have been forgotten or not appreciated [Table 1].

The first ad hoc clinical use of etidronate was in 1968, for treatment of a child with fibrodysplasia ossificans progressiva [7]. After extensive off-label use, the first approved clinical use (oral, 1977) was for treatment of Paget's disease of bone. Other approved indications were heterotopic ossification (oral, 1980) and hypercalcemia of malignancy (intravenous, 1987), with a host of off-label uses (Table 2). Because of its unique properties, it remains the bisphosphonate of choice for treatment of heterotopic ossification but has largely been supplanted by newer (nitrogen-containing) bisphosphonates or other agents for other uses.

2. Paget's disease

Injectable salmon calcitonin was approved by the FDA for treatment of Paget's disease in 1975 but had limited effectiveness and side effects that were sometimes severe. A number of reports of the benefits of etidronate for Paget's disease emerged in the early 1970s [8,9] and etidronate was approved by the FDA for this indication in 1977. Etidronate for Paget's disease was given orally, 5 mg/kg/d, for no longer than 6 months (to reduce the chance of impaired mineralization). Either alone or combined with calcitonin, it reduced the activity of Paget's disease (as reflected by serum alkaline phosphatase determinations) but rarely to normal and the effect was not sustained [10]. Its use for this purpose was quickly supplanted by tiludronate (a more-effective non-nitrogen-containing bisphosphonate and nitrogen-containing bisphosphonates (alendronate, risedronate, zoledronate)).

Table 1
Properties that appear unique to etidronate vs other bisphosphonates,

- High-dose or long-term use inhibits bone mineralization (osteomalacia) [5,6] and interferes with fracture healing
- Increased tubular reabsorption of phosphorus
  - o Hyperphosphatemia
- Increased levels of 1,25-dihydroxyvitamin D
- Increased oxygen carrying capacity of blood
- Absorption is less interfered with by food
  - o Should be given 2 h after and 2 h before food
  - o Has been given to children in orange juice with apparent therapeutic effect
- Does not irritate the esophagus (as nitrogen-containing bisphosphonates do); patients can lie down after taking it

Table 2
Some therapeutic uses of etidronate.

Myositis ossificans[a]	Osteoporosis[b]
Fibrodysplasia ossificans progressiva[a]	Multiple myeloma
Heterotopic ossification[a,b]	Neuropathic arthropathy
Soft tissue calcification[a]	Bone metastases
Medial arterial calcification[a]	Melorheostosis
Paget's disease[b]	Urinary stone disease
Hypercalcemia[b]	Periodontal disease
Osteogenesis imperfecta	Pulmonary microlithiasis
Fibrous dysplasia	Diabetic retinopathy

[a] Conditions where effects on crystallization are important. Others rely on antiresorptive or other effects.
[b] Approved indications in some countries.

3. Osteoporosis studies

In the 1980s, estrogen preparations were commonly used for prevention and treatment of osteoporosis (though never officially approved for “treatment”). Identification of patients was largely limited to those with fractures, as bone densitometry as we know it today was not available. Injectable salmon calcitonin was approved by the FDA for treatment of osteoporosis in 1986 but use was limited by the need for injection as well as side effects, sometimes severe. The data for efficacy of injectable calcitonin for fracture reduction was not robust. (Nasal spray salmon calcitonin was approved in 1995 but again, data for fracture reduction was not strong [11].) At the time of initial approval of calcitonin, the FDA required 2-year placebo controlled trials showing improved bone density and normal bone histology.

“Coherence therapy” for treatment of osteoporosis (Activate-Depress-Free-Repeat) [12] was an attractive hypothesis that might produce anabolic effects on bone. PTH and phosphate were some of the “activating” agents used and etidronate (intermittent – approximately 2 weeks of daily therapy every third month) was used to “depress” osteoclastic bone resorption with hopes of avoiding the mineralization defect. Early work showed somewhat mixed [13] but largely favorable effects of etidronate on bone volume (by biopsy) [14,15], bone mineral density (by dual-photon absorptiometry [DPA]) [16] and fracture rates [17]. At least 2 trials with etidronate for osteoporosis were begun with the FDA 2-year requirement in mind. However, when trials with sodium fluoride appeared to improve bone density but fracture rates were actually increased, regulators at the FDA had second thoughts. Although bone biopsies in the fluoride trial showed abnormal mineralization, failing to meet the (then) criteria, the FDA decided to require 3-year trials with fracture endpoints for approval.

A relatively small study (66 women) from Denmark [18] used etidronate 400 mg/d or placebo for two weeks repeated every 13 weeks (10 cycles) and found increases in bone mineral content (by dual-photon absorptiometry – DPA), a decrease in bone turnover (on biopsy) and a reduction in fracture rates (limited to Weeks 60–150). Bone histology was normal.

An early attempt at studying an ADFR regimen was limited by diarrhea caused by a high dose of phosphate. The authors of the current

paper were involved in (what was originally planned to be) a 2-year Phase 3 study [19] sponsored by Procter & Gamble to investigate cyclic therapy with 1 g of phosphate Days 1–3 followed by 400 mg etidronate Days 4–17 followed by calcium 500 mg Days 18–91 for 8 cycles (4 treatment groups: phosphate/etidronate, placebo/etidronate, phosphate/placebo, placebo/placebo). 429 women were recruited at 7 geographically diverse centers. Although the ADFR concept did not hold up (at least with the agents chosen, which in retrospect were probably not ideal), etidronate (with or without phosphate) resulted in favorable changes in bone density, normal bone histology and as well as a decrease in morphometric vertebral fracture rates. An accompanying editorial said "cyclical etidronate treatment is a welcome new option [for treatment of osteoporosis]" [20].

The writing group for the 2-year paper [19] consisted of Nelson Watts, Steve Harris, Rebecca Jackson and Charles Chesnut, supported by Barb Feiss and Dave Valent of Procter & Gamble and medical writer Cilla Davis. The paper was hammered out in the bucolic and pastoral village of Norwich in upstate New York, home of Norwich-Eaton Pharmaceuticals owned by Procter & Gamble. With nothing much to do in Norwich, the group stayed pretty much on task and were pleased to have been published in the New England Journal of Medicine and received extensive good publicity in the lay press. However, the work was not finished. As the 2-year study was ongoing, it was extended to a third year with hopes of meeting the new FDA requirements, then extended again [21] and again through 7 years (Fig. 2) [22].

Later studies showed similar effects in men with osteoporosis [23] and patients with glucocorticoid-induced osteoporosis [24].

4. Osteoporosis approval process

The US FDA held an Advisory Committee hearing on etidronate in 1995. The day before, the committee recommended approving nasal spray salmon calcitonin for treatment of osteoporosis based on study results that were less than compelling [11]. In the etidronate study, vertebral fracture rates were significantly reduced with treatment from baseline through Month 24 but the difference was no longer significant by Month 36 [21] (in Year 3, there were 18 new fractures in the non-etidronate group and 17 in the etidronate group). This was called "reversal of effect" by some (i.e., benefit in the first 2 years, gone in Year 3), probably incorrectly (in the 7-year data, fracture rates were lower with longer-term treatment [22]). The advisory committee was held on a Friday afternoon, the start was delayed because a morning session ran over and many of the panelists left to get their flights home before the meeting was over. The sponsor's presentation was cut short. Ultimately the panel recommended not to approve etidronate for use in osteoporosis. Some of the participants who voted "no" seemed favorably inclined but "because the drug is already on the market" thought it could still be used "off label" (even though the dosing regimen for osteoporosis was not included in the label). Intermittent cyclic etidronate therapy was approved in 22 other countries with drug regulatory agencies.

5. Reflections

The US study of cyclical etidronate was the first of its kind and laid the foundation for all modern-day Phase 3 trials for osteoporosis – a multicenter trial, protocol developed and refined with input from the investigators with standardized bone density measurements, vertebral fractures assessed by an expert radiologist who developed the semi-quantitative grading scale [25], careful outside monitoring of study centers, a priori definitions of statistical power (but naively assuming that a n of 429 would be sufficient to assess the effect on vertebral fractures and learning that one event could move the p value to 0.051, changing significance to non-significant), transparency of data analysis, effort towards recruiting subjects and maintaining them over several study extensions to get 7 years of data. Given the small number of study centers, there was camaraderie and good will among all investigators that has continued to the present. Given the relatively large number of subjects at each center, there was bonding among the participants as well (and among participants, investigators and study personnel).

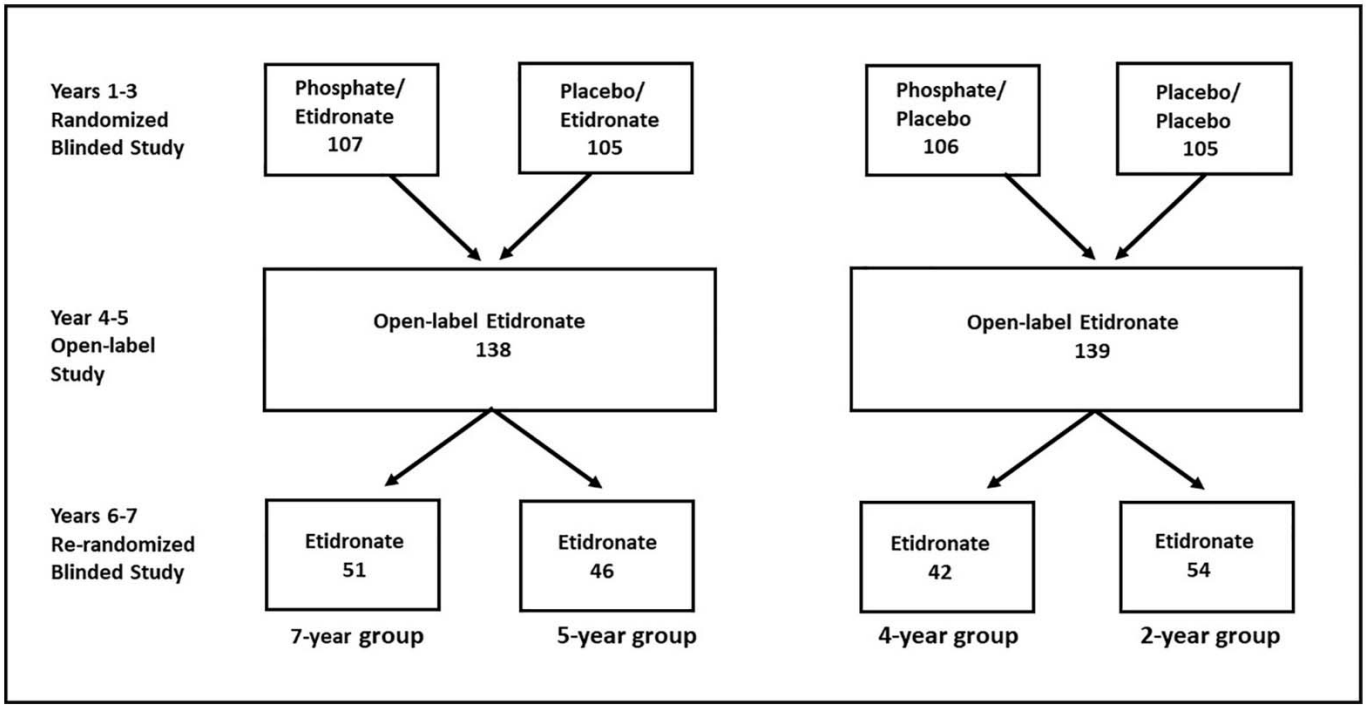

Fig. 2. Timeline of the US study of cyclic etidronate and extension.
From P.D. Miller, N.B. Watts, A.A. Licata, S.T. Harris, H.K. Genant, R.D. Wasnich, P.D. Ross, R.D. Jackson, M.S. Hoseyni, S.L. Schoenfeld, D.J. Valent, C.H.I. Chesnut, Cyclical etidronate in the treatment of postmenopausal osteoporosis: efficacy and safety after 7 years of treatment, Am. J. Med. 103 (1997) 468–476. Used with permission.

The use of etidronate in osteoporosis has largely been supplanted by newer bisphosphonates, which have a much broader therapeutic window (the difference between antiresorptive effect and impaired mineralization). However, it has had a lasting impact on the field of osteoporosis and is still being used for treatment of osteoporosis in some countries (Canada, New Zealand, others).

Acknowledgements

We fondly recall the people at Norwich Eaton and Proctor & Gamble who were involved with the pivotal etidronate study for postmenopausal osteoporosis. Names below are from memory (we apologize if we have forgotten some) and are in alphabetical order: Barb Anderson, Bill Au, Doug Axelrod, Raffaella Balena, Pascale Baudry-Thevenot, John Bevan, Enoch Bortey, Lisa Bosch, Charlotte Brokaw, Kent Buckingham, Shirley Bunn, Mike Burns, Brian Chamberlain, Karen Cooman, Beth Crimmins, Ray D'Alonzo, Reg Dias, Patrick Duntze, Carl Eastwood, Mary Ebert, Frederique Emery-Morel, Liz Ernst, Dominique Ethgen, Barb Feiss, Joy Ferrell, Tom Finn, Robyn Fleming, Dave Francis, Amanda Franklin, Ann Geddes, Pat Hall, Jan Hess, Zeb Horowitz, Marcia Jelus, David Juan, Karin Kirst, Beth Krug, Lori Malloy, Maria Mancini, Lynn Micklas, Mark Meyers, Barbara Miller, Cindy Mitchell, John Nelson, Carrie Nicastro, Carrie Nuzzolese, Donna O'Neal, Chris Orcutt, Perry Owen, Louise Paulsen, Tom Platek, Natalie Quideau, Pam Schofield, Leslie Smith, Greg Stephenson, John Taulbee, Conrad Tou, Flonnie Uhl, Dave Valent, Larry Van Fleet, Bob Wagner, Dave Weber, Loni Weber, Tom Wegman, Mike White.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bone.2020.115222.

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