Correspondence

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Concerning the Paper of J.Y. Reginster Treatment of Bone in Elderly Subjects: Calcium, Vitamin D, Fluor, Bisphosphonates, Calcitonin

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We have read with interest the article of Prof. J.-Y. Reginster entitled ‘Treatment of Bone in Elderly Subjects: Calcium, Vitamin D, Fluor, Bisphosphonates, Calcitonin’ [1], recently published in Hormone Research, and have the following comments regarding bisphosphonates, which have been the subject of studies in our laboratory for the last 9 years.

We think that it would be more useful to classify bisphosphonates on the basis of their potency and therapeutic ratio (effective dose vs. dose which produces side effects) rather than the time of their discovery (first-generation, second-generation, etc). For example, the least potent bisphosphonate, etidronate, was reported to produce osteomalacia [2] at doses used for the treatment of osteoporosis; while pamidronate, although 100-fold more potent, produced GI side effects at therapeutic doses [3]. Since some side effects, such as osteomalacia, are related to the bisphosphonate moiety, they are less likely to occur with more potent compounds, such as alendronate or risendronate.

We noted a significant error in the interpretation of the paper of Apseloff et al. [4] in which tail-suspended rats were treated with alendronate. First of all, the investigators compared tail-suspended treated rats to free-roaming rats, rather than to tail-suspended untreated animals. Furthermore, they compared the 35% increase in bone density in the distal tibia with the 13% increase in bone strength in the diaphysis (the only place where strength was measured by the three-point bending test) and did not take into account that those are different anatomic locations. The strength in the diaphysis could not and should not be affected by the bone mass increase in the distal part of the long bones. In the diaphysis, the increase in strength was 13%, commensurate with the increase in density, about 13%, as expected for normal bone. Furthermore, alendronate has been shown to increase bone strength in direct proportion to bone mass in a large number of studies in different species and treatment protocols. These include: ovariec-tomized rats treated for 6 months [5]; ovari-ectomized baboons treated for 2 years [6]; normal female and male rats treated for 2 years [7]; normal minipigs treated for 1 year [8], and normal female and male dogs treated for 3 years [in press]. I understand that the findings reported in these papers, which have been mailed to Prof. Reginster, have allayed the author’s concern about the safety of alendronate since they
consistently show that the bone accrued by alendronate treatment had normal biomechanical properties, predicting that an increase in bone mineral density produced by alendronate in patients should decrease fracture incidence. In any case, we fully concur with Prof. Reginster that new treatments for osteoporosis should demonstrate statistically significant and clinically meaningful reductions in fracture risk.

With regard to the ‘gastrointestinal in-noceuosness’ of alendronate and other bisphosphonates, a 5-day study period [9] is probably too short to define the safety and tolerability profiles of these agents. In this regard, we note that the overall, and gastrointestinal tolerability of alendronate did not differ from placebo in either the 6-week study cited by Prof. Reginster [10], or in a 1-year study of patients with postmenopausal osteoporosis [11].

References
We agree with our colleagues from the Merck Sharp & Dohme company that bisphosphonates should not be classified on the basis of their time of discovery. However, we do not favor a classification made on the basis of their relative potencies which may considerably vary as a function of the models used to evaluate their antiosteoclastic properties. For example, in vitro, alendronate was reported to inhibit bone resorption at doses 700 times lower than those needed to obtain a similar effect with etidronate [1], while in osteoporotic postmenopausal women, a similar reduction in biochemical markers reflecting bone resorption was obtained with an oral administration of alendronate, 20 mg daily, or etidronate, 400 mg daily [2]. It seems more realistic to classify bisphosphonates on the basis of their chemical structure, and more precisely on the nature of their side chain. This choice also allows one to isolate some clinical characteristics common to particular groups of bisphosphonates like the gastrointestinal intolerance specific to amino-bisphosphonates and reported with pamidronate and alendronate at doses currently used in osteoporosis [3] or Paget’s disease of bone [4]. These effects appear to be related to the chemical nature of the bisphosphonates since they are not or much less described with compounds exhibiting a cyclic ring on the side chain, like tiludronate [5] or risedronate [6].

We do not want to enter into an argument about the paper of Apseloff et al. [7] published and discussed in a peer-reviewed journal. We agree that the subsequent data published by the Merck Sharp & Dohme scientists and quoted in their letter are convincing of an osseous safety of their bisphophonate. However, as a clinician, and taking into account the chronic nature of osteoporosis and the long osseous half-life of bisphosphonates, we consider it essential for all.

References


compounds of this class to clearly demonstrate an anti-fracture efficacy and a long-term local and general safety, at the dose chosen to be administered, on a long-term basis, to postmenopausal women, in agreement with the new recommendations for registration of drugs in the prevention and treatment of osteoporosis in Europe [8].


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