Etidronate for the Neurotologic Symptoms of Otosclerosis: Preliminary Study.

Abstract
The efficacy of etidronate, a bisphosphonate, was assessed as a treatment for the inner ear symptoms of otosclerosis in a retrospective case review of 896 patients diagnosed with otosclerosis, with primary complaints of dizziness, hearing loss, tinnitus or Meniere's syndrome. The diagnosis of otosclerosis was based on small-pixel computed tomography of the temporal bones. Of the 896 patients placed on an etidronate protocol, 545 were followed for more than six months and were analyzed. The symptomatic response to etidronate, as well as audiologic and computerized rotary chair results were used in the assessment. Patients who were previously on sodium fluoride were separately analyzed. In this preliminary study etidronate appeared to be an effective treatment for the neurotologic symptoms of otosclerosis. Prospective blinded efficacy studies of the bisphosphonates in the treatment of otosclerosis should be undertaken.

Introduction
Otosclerosis has been implicated in patients with symptoms of sensorineural hearing loss, tinnitus, dizziness and Meniere's syndrome. The histopathologic basis of otosclerosis leads to an understanding of how clinical neurotologic symptoms occur without evidence of the expected middle ear findings. Otosclerosis is an osseous dyscrasia of the labyrinthine capsule. Findings in the active or the "spongiotic" phase of disorganized bone, rich in osteocytes, include enlarged marrow spaces containing blood vessels and connective tissue, and multinucleated osteoclasts in the center of the lesion absorbing the disorganized bone. These lesions, found anywhere in the otic capsule and oval window, can spread to varying degrees. The healed or "sclerotic" phase is characterized by totally disorganized dense bone with small vascular spaces and no evidence of absorptive
activity. The hair cells appear to be normal. (n40) There are temporal bones with both otosclerotic lesions and endolymphatic hydrops. (n41-n43) The neurotologic symptoms appear to occur via the toxic suppression of hair cell activity by enzymes deposited into the inner ear fluid. (n40) The enzyme theory of inner ear symptoms was first proposed by Wolff and Bellucci in 1960 (n44) and was further expanded by subsequent investigations. (n45-n47) This theory was further evaluated with the use of sodium fluoride by virtue of its effect on rapidly remodeling bone such as that seen in association with spongiotic lesions; reducing the enzymatic activity and thereby arresting the middle ear and inner ear lesions. (n2, n45-n60) Sodium fluoride has been the only recommended medical treatment for otosclerosis. (n49, n57-n59, n61-n68) In the past, the neurotologic symptoms of some patients have responded to the use of fluoride. (n1, n5, n7, n36, n45, n46, n48, n54, n57, n61, n62)

With the advent and availability of the bisphosphonates, etidronate (Didronel) has emerged as a possible treatment for otosclerosis. One paper was published on the agent's potential effect on the middle ear symptoms of otosclerosis, (n69) and another mentions the use of bisphosphonates with "surprisingly good" results, but without mentioning the clinical symptoms treated. (n59) There is experimental evidence suggesting that the bisphosphonates are useful in the treatment of the active phase of otosclerosis. (n70) The purpose of this study was to retrospectively evaluate the use of etidronate to treat the neurotologic symptoms of otosclerosis.

Etidronate is a bisphosphonate primarily indicated for the treatment of Paget's disease of the bone in a continuous dosing schedule. Since 1990, (n118-n120) it has been recommended for the treatment of osteoporosis in a pulsed-dosing schedule.

The bisphosphonates belong to a group of contemporary compounds developed to mimic the naturally occurring substance pyrophosphate. (n121-n123) Bisphosphonates are analogues of pyrophosphates that have a common phosphorus-carbon-phosphorus (P-C-P) chain, making them impervious to breakdown by pyrophosphatases. (n122-n126) They are resistant to cleavage by alkaline phosphate. (n123) Their structure reduces the membrane permeability which accounts for 1-10% of the absorption in the gastrointestinal tract. (n125) Approximately 20-60% of the absorbed bisphosphonate is concentrated in active bone (n122, n125) and the remainder is rapidly excreted unchanged in the urine. (n124) Their chemical structure causes the bisphosphonates to be avidly absorbed onto the surface of hydroxyapatite crystals in bone at sites of active remodeling. (n123, n124) This strong affinity for the calcium phosphate apatite surface inhibits both the formation and dissolution of the crystals (n122) by inhibiting the activity of the osteoclasts when they engulf bisphosphonate-containing minerals during the resorption process. (n122) This is accomplished by local effects and/or by ingestion into the cell, but without destroying the cell. (n124) Implied local effects include inhibition of acid production, lysosomal enzymes, pyrophosphatases and prostaglandin synthesis. (n121, n122) There is also evidence that bisphosphonates, when added to osteoblasts, inhibit osteoblast-stimulating activity. (n127, n128) The serum half-life is about two hours; the half-life in bone is considerably longer. (n122, n123) Etidronate is the only bisphosphonate that inhibits mineralization, (n122, n124) and this is the reason for using a pulsed-dosing schedule.

Methods

Patients

A total of 896 patients from a larger database of patients with otosclerosis-related diagnoses were included in this retrospective case review. There were 356 men and 540 women ranging in age from 18 to 89 years (average 53 years) [Table 1]. Patients presented with primary neurotologic symptoms of dizziness (n=426), (n7, n15, n23, n38, n50, n67, n129) tinnitus (n=152), (n6, n7, n50, n67) sensorineural hearing loss (n=265) (n2, n4, n7, n9, n12,
There was a positive family history of hearing loss, tinnitus and dizziness in 55% of the patients. There was a family history of otosclerosis, a history of otosclerosis surgery or Schwartzte's sign in 9%. Twenty-four percent of the women noted the onset of symptoms in relation to the menarche, the regular menstrual cycle, pregnancy, menopause or the use of hormone replacement therapy. Tympanometry was shallow in 188 patients (21%). Reflexes were diphasic in 33 (4%) and absent in 43 (9%).

Diagnosis

A diagnosis of otosclerosis was suggested upon the basis of history, family history, physical examination and audiometric studies. A prior history of stapedectomy or fenestration strongly points to otosclerosis as the underlying etiology of the neurotologic complaint. Important for an otosclerosis diagnosis is the presentation or exacerbation of symptoms in women at puberty, during pregnancy, lactation and menstruation, during use of contraceptive pills or during menopause. A family history of stapedectomy or fenestration will strongly point to otosclerosis while, in others, there may be a family history of only hearing loss, tinnitus or dizziness. In some patients, Schwartzte's sign can be seen on otoscopy, revealing the hyperemia of the promontory from the accumulation of blood vessels. Audiometry may reveal a mixed hearing loss, suggestive of a conductive component. Also important are the acoustic immittance findings. There may be tympanometry findings of markedly reduced compliance consistent with a stiff ossicular chain but without a conductive hearing loss. The acoustic stapedial reflexes may show the on/off or diphasic findings pathognomonic of an otosclerotic fixed anterior pole of the stapes with a mobile posterior pole and no significant conductive component. Depending upon the middle ear anatomy, the reflexes may be totally absent rather than diphasic, with a sensorineural hearing loss and no conductive component. The most important and confirmatory finding of otosclerosis is in the imaging of the temporal bones. Since the lesions are bony it should be possible with current imaging techniques to visualize most bony changes with respect to density, size or distortion of the described histopathology. The best modality is computed tomography (CT) of the temporal bones.

Prior to 1993, polytomography of the temporal bones was the imaging modality used to identify otosclerosis. Since 1993, small-pixel computed tomography of the temporal bones has been the only diagnostic procedure available to identify otosclerosis. With this resolution, the density of the basal turns of the cochlea, pericochlear lucency, plaques in the poles of the footplate and footplate thickness are easily identified.

For the purposes of this study a diagnosis of otosclerosis was based on the minimal imaging criteria of otosclerosis of the temporal bones. This is accomplished by viewing ultra-thin 1 mm slices of the temporal bone in the axial plane. The Siemens model HiQS scanner was used to evaluate the temporal bones in this study. This scanner uses an extended gray scale to 4000 Hounsfield units (HU) with a pixel matrix of 1024. The exposure was 130 kVolts at 480 mAmmps for four seconds. This produces a small pixel size of 0.07 mm and allows for excellent viewing of the oval and round windows, bony labyrinthine capsule and ossicles. The degree of resolution enables both stapes crura to be seen in the same slice in continuity with the footplate. There are three areas of the otic capsule in which to view the otosclerotic lesions, which may be sclerotic, spongiotic or mixed. First, the poles of the footplate are examined where there is an anterior focus and, less often, a posterior focus. Extending from an anterior focus, there may be plaque formation on the basal
turn to the apex of the cochlea. Next, the footplate is assessed for thickness. It may be normal or thickened to varying degrees. Last, the bony capsule around the cochlea is examined. It may show normal or patchy demineralization or pericochlear lucency. (n13, n107) Previously reported pericochlear lucency seems to occur with thicker slices and/or a larger pixel size. (n117)

Treatment

Etidronate was introduced for use in our patients with a clinical diagnosis of otosclerosis in 1991. Treatment with etidronate was indicated for patients unable to tolerate fluoride preparations or for whom the fluoride preparations did not appear to be effective.

For this study there was no clear-cut dosing schedule for otosclerosis treatment. The Paget's disease protocol called for six months on and six months off the drug in the calendar year and the osteoporosis protocol called for two weeks on and 11 weeks off. The first dose of etidronate for otosclerosis was 400 ma. This was taken daily for two weeks followed by four weeks of supplemental calcium carbonate with vitamin D, and repeated once with the patient returning in three months. If the symptoms improved or stabilized, the duration of treatment with calcium carbonate and the vitamin D supplement was increased to six weeks and the eight-week cycle was repeated before the next visit. If the etidronate was continued beyond seven months, the cycle was changed to two weeks of etidronate and 11 weeks on the calcium carbonate and vitamin D. Some patients responded with an exacerbation of symptoms as the time between administrations of etidronate increased. To prevent the exacerbation, sodium fluoride was reintroduced into the 1 3-week cycle. The patients went on the etidronate for two weeks, and the calcium carbonate and vitamin D supplement for six weeks, followed by sodium fluoride or sodium monofluorophosphate and calcium carbonate for five weeks. The patients were seen at six-month intervals thereafter. Depending upon the symptoms at two years, some dosing variation may be considered or the treatment suspended and the patient observed.

Etidronate was gradually introduced as the primary agent of treatment for the neurotologic symptoms of otosclerosis based on the response of those switched over from the fluoride treatment. This article will also report on those patients switched from the traditional fluoride treatment, and on the difference in the clinical effect achieved.

The objective measurements of improvement in neurotologic function include improvement in symmetry of the rotary chair-induced nystagmus (n139) and significant improvement in hearing (> 15 decibels in pure tones, >15 decibels in speech reception threshold, >16% in speech discrimination).

Results

There were 545 patients seen in follow-up at six months or longer (Table 2). Follow-up ranged from six to 57 months. Initially, the patients were divided into three groups. The first group had less than six months of follow-up and was excluded from analysis because of this short duration. The second group had six to 12 months of follow-up and the third was followed for longer than 12 months (Table 2). The six to 12-month group had 150 patients. The distribution of primary complaints and treatment response of that group was very similar to that of the group of 395 patients followed longer than 12 months, and the two groups were combined.

The response to treatment was divided into three possibilities for each of the presenting symptoms to allow for a spreadsheet analysis (Table 3).
Responses of the group presenting with dizziness were categorized according to the patients' assessment as no change, improved or asymptomatic. There were 19 patients (7\%) who reported no change, meaning that the dizziness was the same or worse on the etidronate. Patients whose dizziness improved (145 [54\%]) reported that symptoms were better, caused little or no disability and, while tolerable, dizziness was not completely gone. Asymptomatic patients were those with no dizziness symptoms (103 [39\%]). There were 230 patients in whom computerized rotary chair testing was performed. Testing was performed at the three-month visit or sooner, unless normal symmetry was noted as part of an original vestibular evaluation. There was normal symmetry in 115 (59\%) patients. Symmetry improved from abnormal to normal in 68 (35\%) patients, and remained abnormal in 12 (6\%). These percentages paralleled the patients' self-evaluations.

Patients assessed their hearing loss in three categories: no change, improved or normal. No change in a patient with progressive sensorineural hearing loss was an improvement over pretreatment status. There were 44 patients (27\%) in this group, 114 (70\%) in the improved group and two (4\%) who improved to normal hearing. There were 103 patients for whom hearing results were available for comparison. Hearing was the same in 73 (71\%), better in 28 (27\%) and worse in two (2\%).

The tinnitus response was categorized as no improvement, improved or asymptomatic. There were 22 (32\%) patients in whom the tinnitus was uncharged, 36 (52\%) in whom tinnitus was improved (still present but tolerable) and 11 (16\%) in whom the tinnitus disappeared.

Response among the patients with Meniere's syndrome was assessed as no change, improved or asymptomatic. There were six patients (13\%) with no change in symptoms. It is of note that when the "no change" group was analyzed the numbers fell from 23\% in the six to 12-month follow-up group to 9\% in the longer than 12-month follow-up group. An "improved" response was defined as less frequent episodes of shorter duration and lesser severity, producing a tolerable situation allowing near-normal functional status for work and social activities. There were 15 patients (32\%) in this group. There were 26 (55\%) patients who were asymptomatic. Computerized rotary chair testing was available in 35 patients. Normal symmetry was found in 24 (69\%), improved symmetry in eight (23\%), and abnormal symmetry in three (9\%). Hearing tests were available in 46 of these Meniere's syndrome patients. Hearing was the same in 23 (50\%) patients, improved in 14 (30\%) patients, and worse in nine (20\%) patients.

There were 186 patients who were switched from sodium fluoride alone to etidronate for whom there was follow-up of six months or longer (Table 4). These patients were switched because the fluoride failed to control the symptoms, because of adverse effects or to see if a better result could be achieved with etidronate. Of the 85 patients with a primary complaint of dizziness, 47 (55\%) were improved and 32 patients (38\%) were asymptomatic. Of the 61 patients with a primary complaint of sensorineural hearing loss, 17 (28\%) had no change in hearing and 43 patients (70\%) were improved. Of the 17 patients with a primary complaint of tinnitus, 10 were improved and tinnitus disappeared in three. Of the 23 patients with Meniere's syndrome, nine were improved and 11 were asymptomatic.

**Discussion**

The diagnosis of neurotologic disorders secondary to otosclerosis is controversial. Much of the controversy seems to stem from the perceived inability to make a diagnosis of otosclerosis without conductive hearing loss. Imaging technology advances with small-pixel computed tomography of the temporal bones now provide the resolution necessary to make a diagnosis of otosclerosis. The literature is replete with information supporting the
concept of inner ear disorders secondary to labyrinthine otosclerosis. Since experience revealed a beneficial response to the use of fluoride (n1, n4-n6, n47, n50, n59, n64, n92, n140) the concept of treating inner ear otosclerosis with a bisphosphonate seemed reasonable.

It was decided to analyze the data beginning at six months. As the data were being collected, there was a large group of patients (351) who were not seen at six months or beyond. Closer examination of this group revealed that many had returned at three months, as required in the protocol, and were significantly better or asymptomatic, possibly feeling that further follow-up was unnecessary. Included in this group were 83 patients with tinnitus, comprising 55% of all the tinnitus patients. The failure to follow-up in this tinnitus group may represent an inadequate subjective response to the treatment over this period of time.

The collated data for the patients who returned between six and 12 months were analyzed. It was apparent that this group of 150 patients was responding to the regimen in the respective diagnostic categories in similar numbers to those in the group with more than 12 months of follow-up. The only changes in response were the decreasing numbers of poor responders as the treatment duration increased.

The group of patients previously on fluoride treatment was examined. Analysis of this group is important because many of the patients treated with etidronate were also treated for concomitant metabolic disorders, possibly affecting the inner ear. This group of 186 patients, which was switched from fluoride to etidronate, acted as their own controls with respect to a concurrent treatment. The clinical results were similar to those of the larger group.

**Conclusions**

The results of this preliminary study support the theory that the etidronate effect reduces the osteoclastic activity in otosclerotic lesions, thus reducing the enzyme level in the inner ear fluids and the toxicity of the hair cells.

In 1991 etidronate was the only bisphosphonate available and papers were appearing in the literature describing its application for osteoporosis. (n119, n141, n142) The results of this preliminary study reveal that etidronate can effectively halt the decline and sometimes rapidly reverse the symptoms of abnormal inner ear function. As the pulsed-dosing schedule is lengthened the response of the inner ear may lessen, as seen in some of our patients. It is suggested that these otosclerotic lesions require the effect of an additional active agent such as fluoride to sustain the clinical effect of the etidronate. Fluoride salts affect bone by stimulating osteoblastic function. (n143, n144)

**Summary**

In patients with neurotologic complaints, ultra-thin, small-pixel computed tomography of the temporal bones should be performed to visualize otosclerosis. The bisphosphonate, etidronate, used in an appropriate dosing schedule, appears to be a more effective treatment for the neurotologic symptoms of otosclerosis than sodium fluoride alone. Future investigation on this subject should be centered on:

1. The minimum technical specifications required for the radiologic diagnosis of otosclerosis with high-resolution computed tomography scanners;
2. Evaluation of the subsequent generation of bisphosphonates and their potential role in the treatment of the symptoms of otosclerosis;
3. Development of blinded studies of the bisphosphonates in patients with appropriate clinical diagnoses; and
4. A detailed follow-up survey on the group of bisphosphonate-treated patients with less than six months of follow-up.

**Acknowledgment**

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**Table 1. Initial Symptoms by Gender.**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>41%</td>
<td>52%</td>
<td>426</td>
</tr>
<tr>
<td>Hearing Loss</td>
<td>32%</td>
<td>28%</td>
<td>265</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>20%</td>
<td>15%</td>
<td>152</td>
</tr>
<tr>
<td>Meniere's</td>
<td>7%</td>
<td>5%</td>
<td>53</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>356</td>
<td>540</td>
<td>896</td>
</tr>
</tbody>
</table>

**Table 2. Follow-up Breakdown.**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>&lt;6 Months</th>
<th>6-12 Months</th>
<th>&gt;12 Months</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>159</td>
<td>81</td>
<td>186</td>
<td>426</td>
</tr>
<tr>
<td>Hearing Loss</td>
<td>103</td>
<td>31</td>
<td>131</td>
<td>265</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>83</td>
<td>26</td>
<td>43</td>
<td>152</td>
</tr>
<tr>
<td>Meniere's</td>
<td>6</td>
<td>12</td>
<td>35</td>
<td>53</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>351</td>
<td>150</td>
<td>395</td>
<td>896</td>
</tr>
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</table>

**Table 3. Response by Initial Symptom.**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No Change</th>
<th>Improved</th>
<th>Asymptomatic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>19 (7%)</td>
<td>145 (54%)</td>
<td>103 (39%)</td>
<td>267</td>
</tr>
<tr>
<td>Hearing Loss</td>
<td>44 (27%)</td>
<td>114 (70%)</td>
<td>4 (2%)</td>
<td>162</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>22 (32%)</td>
<td>36 (52%)</td>
<td>11 (16%)</td>
<td>69</td>
</tr>
<tr>
<td>Meniere's</td>
<td>6 (13%)</td>
<td>15 (32%)</td>
<td>26 (55%)</td>
<td>47</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>91</td>
<td>310</td>
<td>144</td>
<td>545</td>
</tr>
</tbody>
</table>

**Table 4. Response Compared to Fluoride.**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No Change</th>
<th>Improved</th>
<th>Asymptomatic</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>6 (7%)</td>
<td>47 (55%)</td>
<td>32 (38%)</td>
<td>85</td>
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<tr>
<td>Hearing Loss</td>
<td>17 (28%)</td>
<td>43 (70%)</td>
<td>1 (2%)</td>
<td>61</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>4 (24%)</td>
<td>10 (58%)</td>
<td>3 (18%)</td>
<td>17</td>
</tr>
<tr>
<td>Meniere's</td>
<td>3 (13%)</td>
<td>9 (39%)</td>
<td>11 (48%)</td>
<td>23</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>30</td>
<td>109</td>
<td>47</td>
<td>186</td>
</tr>
</tbody>
</table>

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References


(n18.) Linthicum FHJ. Correlation of sensorineural hearing impairment and otosclerosis. Tr Am Otol Soc...
1966;54:155-68.


(n23.) McCabe BF. Otosclerosis and vertigo. Trans Pac Coast Otoophthalmol Soc 1966; 47:37-42.


(n35.) Shambaugh G. Sensorineural hearing loss due to cochlear otospongiosis: Pathogenesis, clinical


(n44.) Wolff D, Bellucci R. The histopathology observed in fifty biopsied stapedes. Trans Amer Acad Ophth Otolaryngol 1960; (July-August):540-53.


(n64.) Shambaugh GEJ, Scott A. Sodium fluoride for the arrest of otosclerosis. Arch Otolaryngol 1964; 80:263.


(n70.) Petrovic AG, Stutzman JJ. Diphosphonates: A potential medication for evolutive otospongiosis, in Donath...


(n73.) Smith HW. Effect of pregnancy on otosclerosis. AMA Arch Otolaryngol 1948; 48:159.


(n85.) Graham AB. An audiological and otological investigation of normal hearing individuals with a family history of otosclerosis. Chicago, Northwestern University PhD Thesis, 1953


(n88.) Causse JR, Causse JB. Otospongiosis as a genetic disease. Early detection, medical management and


(n105.) Altmann F, Kornfeld M, Shea JJ. Inner ear changes in otosclerosis. Histopathological studies. Ann Otol
Rhinol Laryngol 1966; 75:129.


(n123.) Ott S. Clinical effects of bisphosphonates in involutional osteoporosis. J Bone Min Res 1993; 8(Suppl


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