Six-Month Treatment With Alendronate in Acute Charcot Neuroarthropathy

A randomized controlled trial

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Charcot neuroarthropathy is defined by painful or relatively painless bone and joint deformity in limbs that have lost sensory innervation (1). The incidence is ~0.1–5% in diabetic patients with peripheral neuropathy (2,3). The pathogenesis of Charcot neuroarthropathy is unknown (1,4). In acute Charcot neuroarthropathy, osteoclast activity increases (5). Alendronate is a bisphosphonate that induces the apoptosis of the osteoclasts (6). The utilization of the alendronate could improve the clinical signs of acute Charcot neuroarthropathy and stop bone resorption.

**RESEARCH DESIGN AND METHODS** — A total of 20 consecutive patients with a new diagnosis of acute painful Charcot neuroarthropathy were enrolled after the approval of the ethics committee. The patients gave informed consent. Acute Charcot neuroarthropathy was defined on the basis of at least three of the following clinical signs: edema, erythema, and skin temperature increase of 2°C compared with contralateral foot (temperature was measured using an infrared thermometer [Riester] at the site of maximum deformity of the affected foot [9] were done to obtain a differential diagnosis with osteomyelitis.

Serum collagen COOH-terminal telopeptide of type 1 collagen (ICTP), osteocalcin, testosterone, estradiol, thyroid hormones, parathyroid hormone, follicle-stimulating hormone, and leutinizing hormone were measured in serum by immunoassay in electrochemiluminescence (Roche, Montclair, NJ).

IGF-1 and calcitriol were measured by chemiluminescence (Nichols), estron by immunoradiometric assay (Immuno- tech Beckman, Fullerton, CA), and urinary hydroxyprolin through high-performance liquid chromatography (Biorad, Richmond, CA) from 24-h urine collection.

Serum alkaline phosphatase was measured by colorimetric assay (Roche- Hitachi) and serum bone alkaline phosphatase by electrophoretic method (Isopal Sebia ITA). Bone mineral density (BMD) measurements of the lumbar spine (L2-L4), proximal femur, and feet were performed by dual-energy X-ray absorptiometry using a Hologic QDR 2000 densitometer. The affected foot was manually positioned on the scan table and the scan started at the toes and moved toward calcaneous. The software used for the lumbar spine was digitally applied to the foot scan. Determination of size and location of the region of interest (phalanx, tarsus, or metatarsus) was made manually, and the measure of the BMD of the single region of interest was determined automatically by the spinal software. Reproducibility was assessed by taking 10 repeated measurements; the foot was moved and repositioned between measurements. ANOVA was used to compare the test group and the control group. Significance was set at P < 0.05.

**RESULTS** — All patients had a Neuropathy Disability Score >5 (10), a pathological conduction velocity, a vibration perception threshold >25 volts (11), and an autonomic neuropathy according to Ewing and Clarke with a score >4 (12). No subjects had osteomyelitis or peripheral vascular disease (defined as an ankle-brachial index of <0.9) throughout the study (Table 1). The midfoot was the most affected. Five patients had unaffected foot ulcers (cultures of debrided tissue were always negative) that healed during the study.

ICTP did not show significant difference between the two groups (0.54 ± 0.05 vs. 0.56 ± 0.06 ng/ml, P < 0.6) at the outset, but after 6 months, the test
group showed a significant decrease (0.54 ± 0.05 vs. 0.30 ± 0.03 ng/ml, P < 0.05). In the test group, hydroxyprolin followed the same trend (18 ± 3.2 vs. 13 ± 3.6 mg/l, P < 0.05). Bone alkaline phosphatase reduction was almost significant (36 ± 4.8 vs. 23 ± 3.9%, P = 0.06). Dual-energy X-ray absorptiometry demonstrated an improvement in total foot mineralization (0.18 ± 0.06 vs. 0.24 ± 0.08 g/cm², P < 0.05) and in the distal phalanxes (0.194 ± 0.03 vs. 0.242 ± 0.05 g/cm², P < 0.01) in the test group that had an improvement of the mineralization of the femur. VAS score for pain was significantly improved in the test group (6.5 ± 0.9 vs. 4.2 ± 0.8, P < 0.05). No significant changes were evident in the control group (6.7 ± 1 vs. 6.1 ± 1.1).

At the outset, the affected foot was 3.6 ± 1.1°C hotter in the test group and 3.4 ± 1.2°C hotter in the control group. After 6 months, both groups had a significant improvement (~1.7°C in the test group and ~1.5°C in the control group). Reduction of IGF-1 was observed only in the test group (142.8 ± 24 vs. 123.5 ± 41 ng/ml, P < 0.05). No side effects were reported.

**CONCLUSIONS** — This study is based on the utilization of alendronate taken by mouth to stop the progression of Charcot neuroarthropathy (13). After 6 months, we showed that there is a significant reduction of ICTP and hydroxyprolin, markers indicative of bone reabsorption. The test group showed an increase of the foot bone density compared with the control group that was more evident in the distal phalanxes, which were the foot bones with the lowest BMD, than in the midfoot. We suppose that bisphosphonates are more effective where bone reabsorption is more marked. The significant reduction of IGF-1 levels in the test group could improve bone density, lowering the blood supply to bones (14).

Off-loading, which reduces inflammation, together with alendronate, which decreases the cytokine production within the bones of the foot, could explain the reduction of pain (15,16). Furthermore, bisphosphonates have a central antinociceptive effect connected with the Ca²⁺ mechanism. Ca influx releases substances involved in nociception and inflammation, such as substance P, vasoactive intestinal peptide, neuropeptide Y, prostaglandin, serotonin, and kinines (17–19). We did not detect the initial fall of the temperature linked to the bisphosphonates because we checked it at the beginning and end of the study (20). In conclusion, we observed a clinical improvement of acute Charcot neuroarthropathy by using alendronate.

**Table 1—Test group results**

<table>
<thead>
<tr>
<th>Test group results</th>
<th>At the outset</th>
<th>After 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICTP (ng/ml)</td>
<td>0.56 ± 0.06</td>
<td>0.30 ± 0.03</td>
</tr>
<tr>
<td>Urinary hydroxyprolin (mg/l)</td>
<td>18 ± 3.2</td>
<td>13 ± 3.6</td>
</tr>
<tr>
<td>BMD foot (g/cm²)</td>
<td>0.18 ± 0.06</td>
<td>0.24 ± 0.08</td>
</tr>
<tr>
<td>BMD distal phalanxes (g/cm²)</td>
<td>0.194 ± 0.03</td>
<td>0.242 ± 0.05</td>
</tr>
<tr>
<td>VAS pain score</td>
<td>6.5 ± 0.9</td>
<td>4.2 ± 0.8</td>
</tr>
<tr>
<td>IGF-1 (ng/ml)</td>
<td>142.8 ± 24</td>
<td>123.5 ± 41</td>
</tr>
</tbody>
</table>

Data are means ± SD.