The relief of bone pain in primary biliary cirrhosis with calcium infusions

A. B. AJDUKIEWICZ, J. E. AGNEW, P. D. BYERS, M. R. WILLS, AND SHEILA SHERLOCK

From the Departments of Medicine, Physics, and Chemical Pathology, Royal Free Hospital, London, and the Institute of Orthopaedics, London

SUMMARY

Intravenous calcium infusions produced subjective relief of bone pain in 14 patients with primary biliary cirrhosis. The bone pain had developed despite long-term parenteral vitamin D therapy. The pain returned after two to three months, but a subsequent course of infusions again brought relief. Before treatment satisfactory iliac crest bone biopsies were obtained in 11 of the patients and were normal in seven; two patients had biopsies indicating osteomalacia and two osteoporosis. After treatment a repeat biopsy in one of the patients with osteomalacia showed marked reduction in osteoid. The infusion treatment produced no change in plasma calcium concentration, serum phosphate, or serum alkaline phosphatase. Absorption of oral calcium was also unchanged.

Metabolic bone diseases, both osteoporosis and osteomalacia, complicate hepato-biliary disorders (Atkinson, Nordin, and Sherlock, 1956; Lichtwitz, Cachin, Hioco, Tutin, and de Sèze, 1959). Osteomalacia is characterized by a diminished volume of bone and is the end result of many processes. Osteomalacia is a disease produced by a lack of cholecalciferol (vitamin D₃) and its biologically active metabolites, and is manifested in bone by reduced mineralization and excessive amounts of osteoid. Bone pain in patients with primary biliary cirrhosis may be due to osteomalacia, osteoporosis with or without fractures, and rarely to periosteal reactions.

Despite the administration of parenteral vitamin D some patients with primary biliary cirrhosis develop bone pain either in association with osteomalacia, fractures, and periosteal reactions or, rarely, in the absence of these findings. Pak, Zisman, Evens, Jowsey, Delea, and Bartter (1969) treated six patients with idiopathic osteoporosis and fractures using intravenous calcium infusions. They reported improvement both clinical and in calcium retention, bone formation was enhanced, bone resorption reduced, and gastrointestinal calcium absorption increased. In view of these findings the present study was undertaken to investigate the effect of intravenous calcium infusions in 14 patients with primary biliary cirrhosis who complained of bone pain, all of whom had received parenteral vitamin D. Plasma calcium and phosphate concentrations, plasma alkaline phosphate activity, and intestinal calcium absorption were measured and bone biopsies performed.

Methods

CALCIUM INFUSION

Each patient received a calcium infusion daily for 12 consecutive days. Each infusion consisted of calcium gluconate diluted in 5% dextrose to about 500 ml and administered intravenously over four hours. The dose of calcium was 1·5 mg/kg body weight (low dose) or 15 mg/kg body weight (high dose).

In seven patients a pulse of 10 μCi ⁴⁷Ca was added to the first infusate. The activity remaining in the drip bottle and tubing was checked. The fate of the pulse was followed by stool and urine collections, and in six patients by whole body counting.

CALCIUM ABSORPTION

Retention of ⁴⁷Ca was measured by a simple single crystal whole body counter which has been shown to provide a good index of ⁴⁷Ca absorption (Agnew, Kehayoglou, and Holdsworth, 1969). Ten μCi
Excess osteoid was taken as indicating osteomalacia, excess resorption as indicating hyperparathyroidism, and reduced bone volume as indicating osteoporosis.

**BIOCHEMISTRY**
Calcium in plasma and urine was determined by atomic absorption spectrophotometry and other biochemical determinations were performed by routine laboratory methods.

**PATIENTS STUDIED**
The 14 patients were all suffering from primary biliary cirrhosis diagnosed according to recognized criteria (Sherlock and Scheuer, 1973; Sherlock, 1974). They were all female and the duration of illness was from two to 10 years (table I). None of the patients was suffering from portosystemic encephalopathy. Fluid retention was present in seven patients.

All the patients complained of backache and also had pain in the arms, legs, or ribs. Apart from case 7, they had all received intramuscular vitamin D3, 100,000 iu every month for one to seven years. Fractures (table I) were present in seven patients. There was no evidence of thyroid or pituitary-adrenal axis dysfunction as assessed by estimation of serum T3, serum thyroxine and circadian cortisol studies; nor was there any evidence of renal tubular dysfunction as evidenced by urine amino acid chromatography. Blood urea was normal in all patients.

The dietary intake of calcium and of protein was similar in the infused patients to that of patients of similar ages suffering from non-biliary chronic

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (years)</th>
<th>Duration of Illness (years)</th>
<th>Vitamin D3 (years)</th>
<th>Fluid Retention (months)</th>
<th>Site of Bone Pain</th>
<th>Bilirubin (mg/100 ml)</th>
<th>Alkaline Phosphate (K.A. units/100 ml)</th>
<th>Total Protein (g/100 ml)</th>
<th>Albumin</th>
<th>Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>7</td>
<td>4½</td>
<td>1</td>
<td>Back, elbows, ankles</td>
<td>15.0</td>
<td>34</td>
<td>7.0</td>
<td>3-3</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>Back, elbows, knees, shins</td>
<td>14.0</td>
<td>40</td>
<td>7-3</td>
<td>3-1</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>Back, elbows, ankles</td>
<td>12.0</td>
<td>156</td>
<td>6.5</td>
<td>3-3</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>68</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td>Back, arms, legs</td>
<td>4.0</td>
<td>36</td>
<td>6-4</td>
<td>2-3</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>64</td>
<td>7</td>
<td>5</td>
<td>0</td>
<td>Back, feet, hands</td>
<td>21.0</td>
<td>320</td>
<td>7-4</td>
<td>3-2</td>
<td>Collapse T12 and L2</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>6</td>
<td>1</td>
<td>9</td>
<td>Back, arms</td>
<td>36.5</td>
<td>90</td>
<td>7-1</td>
<td>2-6</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>51</td>
<td>2</td>
<td>Nil</td>
<td>0</td>
<td>Back, knees, shins, ankles</td>
<td>1-7</td>
<td>62</td>
<td>7-4</td>
<td>4-2</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>56</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>Back, hips, hands</td>
<td>0-4</td>
<td>52</td>
<td>7-9</td>
<td>4-1</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>54</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>Back, arms, shins</td>
<td>9-0</td>
<td>50</td>
<td>8-5</td>
<td>3-3</td>
<td>Right neck femur</td>
</tr>
<tr>
<td>10</td>
<td>62</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>Back, ribs, legs</td>
<td>8-5</td>
<td>96</td>
<td>6-6</td>
<td>3-1</td>
<td>Right humerus</td>
</tr>
<tr>
<td>11</td>
<td>57</td>
<td>8</td>
<td>7</td>
<td>6</td>
<td>Back, arms, legs</td>
<td>21.5</td>
<td>40</td>
<td>7-7</td>
<td>3-4</td>
<td>Ribs, ramus pubis</td>
</tr>
<tr>
<td>12</td>
<td>65</td>
<td>5</td>
<td>4</td>
<td>24</td>
<td>Back, arms, legs</td>
<td>20-5</td>
<td>160</td>
<td>8-5</td>
<td>3-4</td>
<td>Ribs, sternum</td>
</tr>
<tr>
<td>13</td>
<td>63</td>
<td>2</td>
<td>1½</td>
<td>6</td>
<td>Back, shoulders</td>
<td>6-4</td>
<td>80</td>
<td>7-0</td>
<td>3-0</td>
<td>Collapse vertebral</td>
</tr>
<tr>
<td>14</td>
<td>56</td>
<td>4</td>
<td>3½</td>
<td>6</td>
<td>Back, shoulders, shins</td>
<td>21-5</td>
<td>110</td>
<td>7-6</td>
<td>2-6</td>
<td>Collapse vertebral</td>
</tr>
</tbody>
</table>

Table I  Clinical and biochemical findings in the patients with primary biliary cirrhosis studied
Table II  Clinical and biochemical response to low-dose calcium infusion therapy

liver disease. Five patients were only taking about 40 g of protein.

Results

In no patient did any untoward symptom necessitate stopping treatment. Two patients (cases 2 and 7) complained of nausea, in case 2 accompanied by headache, towards the end of the last three days of high dose infusion treatment.

Blood urea concentrations were normal both before and after treatment. In none was there any change in plasma creatinine concentration nor was there any change in endogenous creatinine clearance.

Throughout the treatment the patients were never questioned about bone pains until they themselves referred to the subject. In fact all patients volunteered the information that the bone pain was diminishing. Pain, judged by the patient's reactions, was relieved in three to 12 days from the onset of infusions and the relief lasted for two to three months. The relief of bone pain was achieved more rapidly using the high dose infusions, but there was no difference in the duration of remission despite the variation in dose (tables II and III).

Six patients died within three months of having the calcium infusion, reflecting the advanced stage of the disease of the patients studied. Five patients had repeated infusions.

Plasma calcium concentrations had not altered significantly on the day following the infusion

Table III  Clinical and biochemical response to high-dose calcium infusion therapy

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Total Calcium Infused (g)</th>
<th>Ca (mg 100 ml)</th>
<th>PO₄ (mg 100 ml)</th>
<th>AP (K.A. units 100 ml)</th>
<th>After Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Over 112 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.82</td>
<td>7.8</td>
<td>3.8</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.78</td>
<td>8.4</td>
<td>3.3</td>
<td>156</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.86</td>
<td>9.0</td>
<td>4.8</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.67</td>
<td>9.0</td>
<td>2.5</td>
<td>280</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Total Calcium Infused (g)</th>
<th>Ca (mg 100 ml)</th>
<th>PO₄ (mg 100 ml)</th>
<th>AP (K.A. units 100 ml)</th>
<th>After Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Over 112 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.82</td>
<td>7.8</td>
<td>3.8</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.78</td>
<td>8.4</td>
<td>3.3</td>
<td>156</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.86</td>
<td>9.0</td>
<td>4.8</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.67</td>
<td>9.0</td>
<td>2.5</td>
<td>280</td>
<td></td>
</tr>
</tbody>
</table>

Table III  Clinical and biochemical response to high-dose calcium infusion therapy

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Total Calcium Infused (g)</th>
<th>Ca (mg 100 ml)</th>
<th>PO₄ (mg 100 ml)</th>
<th>AP (K.A. units 100 ml)</th>
<th>After Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Over 112 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.82</td>
<td>7.8</td>
<td>3.8</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.78</td>
<td>8.4</td>
<td>3.3</td>
<td>156</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.86</td>
<td>9.0</td>
<td>4.8</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.67</td>
<td>9.0</td>
<td>2.5</td>
<td>280</td>
<td></td>
</tr>
</tbody>
</table>
The relief of bone pain in primary biliary cirrhosis with calcium infusions

CALCIUM ABSORPTION

Before treatment calcium absorption as measured by retention was subnormal in six patients (see fig). In patient 10, with marked osteomalacia, retention rose from 14 to 25%: the other patients showed little change.

BONE BIOPSIES (TABLE IV)

In seven patients (cases 1, 3, 4, 7, 8, 13, and 14) bone biopsies were essentially normal. One further patient (case 2) was also probably normal although the specimen was fragmented.

Two patients (cases 10 and 11) showed osteomalacia, in one of whom (case 11) bone volume was low. Patient 10 had very striking osteomalacia despite a year's vitamin D treatment. At necropsy one year later, the iliac crest was classified as only possible osteoporosis. In other bones studied at necropsy (skull, rib, vertebra, and femoral shaft) bone volume was not so obviously reduced and osteoid was within normal limits. The second patient (case 11) was less definitely osteomalacic in that surface coverage was just within normal limits and osteoid mineralization was not obviously altered—but the osteoid area was high.

Two patients (cases 9 and 12) showed osteoporosis. Case 12 had extremely low osteoid levels before and after treatment, together with active, normal, and possibly increasing, resorption. This makes the decrease in bone area from 10 to 5% appear a real one—indicating a progressive osteo-

treatment. In those on high dose infusion there was a mean rise of 0.12 mg/100 ml and on low dose a mean fall of 0.25 mg/100 ml (tables II and III).

---

**Fig** Effect of calcium infusions (iv) on calcium retention

<table>
<thead>
<tr>
<th>Case</th>
<th>Iliac Crest</th>
<th>Osteoid</th>
<th>Resorption</th>
<th>Bone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% Surface</td>
<td>% Area</td>
<td>% Surface</td>
</tr>
<tr>
<td>1</td>
<td>Pre</td>
<td>&lt;10</td>
<td>&lt;1</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>Pre</td>
<td>&lt;10</td>
<td>&lt;1</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>&lt;10</td>
<td>&lt;1</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>Pre</td>
<td>&lt;10</td>
<td>&lt;1</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>Pre</td>
<td>&lt;10</td>
<td>&lt;1</td>
<td>&gt;5</td>
</tr>
<tr>
<td>8</td>
<td>Pre</td>
<td>&lt;10</td>
<td>&lt;1</td>
<td>12</td>
</tr>
<tr>
<td>9</td>
<td>Pre</td>
<td>&lt;10</td>
<td>Unsatisfactory</td>
<td>Biopsy</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>Pre</td>
<td>99</td>
<td>&gt;1 (11%)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>&lt;10</td>
<td>&lt;1 (0-5%)</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>Pre</td>
<td>25</td>
<td>&gt;1 (2%)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>&lt;10</td>
<td>&lt;1 (0-1%)</td>
<td>15</td>
</tr>
<tr>
<td>12</td>
<td>Pre</td>
<td>&lt;10</td>
<td>&lt;1</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>&lt;10</td>
<td>&lt;1</td>
<td>12</td>
</tr>
<tr>
<td>13</td>
<td>Pre</td>
<td>&lt;10</td>
<td>&lt;1</td>
<td>25</td>
</tr>
<tr>
<td>14</td>
<td>Pre</td>
<td>&lt;10</td>
<td>&lt;1</td>
<td>25</td>
</tr>
</tbody>
</table>

**Table IV** Results of bone biopsy before treatment (pre) and after (post) infusion therapy

All the figures are approximate but accurate enough to indicate levels above or below critical values (see text).

*
oporosis due to reduced formation and active, but
normal, resorption. In case 9 the pretreatment
biopsy was too small for quantitation although its
fragmented nature suggested osteoporosis. After
treatment postmortem study showed no osteoid
and marked osteoporosis in all the bones examined
(iliac crest, a lumbar vertebra, rib, and femur).

**Retention of Infusate**
Six patients had \(^{47}\)Ca pulse labelling of the infusion
on the first day of a treatment course (Table V).
Two of these patients had normal absorption of an
oral \(^{47}\)Ca dose before the infusion (cases 7 and 8).
These two showed the highest \(^{47}\)Ca urinary excre-
tion and lowest whole body retention. In contrast
the lowest urinary excretion and highest whole
body retention was seen in the patient with early
osteomalacia (case 11).

<table>
<thead>
<tr>
<th>Case No.</th>
<th>3</th>
<th>4</th>
<th>7</th>
<th>8</th>
<th>11</th>
<th>13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twelve-day retention by whole body counting (%)</td>
<td>38</td>
<td>36</td>
<td>24</td>
<td>20</td>
<td>72</td>
<td>47</td>
</tr>
<tr>
<td>Percentage of dose in urine in 12 days</td>
<td>28</td>
<td>29</td>
<td>41</td>
<td>46</td>
<td>11</td>
<td>21</td>
</tr>
</tbody>
</table>

**Table V Retention of \(^{47}\)Ca Infusate**

**Discussion**
In all 14 patients with primary biliary cirrhosis
calcium infusions induced relief of bone pain.
This occurred within three to 12 days of starting
the infusions and lasted for two to three months,
when a subsequent course of infusions was again
effective. There were no serious complications.
The absence of side effects was consistent with
the small and unsustained increases in plasma calcium
concentration.

In spite of regular parenteral vitamin D treatment
gastrointestinal calcium absorption, as measured
by retention, was subnormal in six patients. This
was unaffected by the infusions. These findings are
not in agreement with those of Pak et al (1969)
who reported an improvement in intestinal calcium
absorption after calcium infusion treatment in
four of their osteoporotic patients who were re-
sponsive to treatment with no significant change in
the other two who were unresponsive. A lack of
effect on intestinal calcium absorption with calcium
infusion treatment could, however, be expected
from a consideration of the factors involved in
intestinal calcium absorption, the most important
factor in which is 1,25-dihydroxycholecaliferol
(Wills, 1973). The rate of renal synthesis of this
steroid hormone is under feed-back control; the
likely determinant would appear to be intracellular
calcium concentration (Galante, Colston, Evans,
Byfield, Matthews, and MacIntyre, 1973). It was
expected that calcium infusions would, through
the feed-back control mechanism, tend to reduce
the rate of renal synthesis of 1,25-dihydroxychole-
calciferol with a consequent decrease rather than
increase in intestinal calcium absorption.

Two of the patients had histological evidence of
osteomalacia, despite long-term intramuscular vita-
mn D therapy. In one of these two patients a bone
biopsy after treatment showed healing of the osteo-
malacia. In the 14 patients studied this constitutes
the only objective evidence of a beneficial effect of
the infusions. Healing of osteomalacia was also
seen in a further patient with secondary biliary cirrhosis
whose pain was relieved by infusion treatment.

The retention of radiocalcium-labelled infusate,
and presumably infused calcium, showed wide
variations between patients. One patient with
osteomalacia appeared to have an exceptional
avidity for infused calcium—retaining 72% of the
infused radioisotope after 12 days. A similar result
was found in the patient with secondary biliary
cirrhosis and osteomalacia. These high retentions,
with corresponding low urinary outputs, resemble
the results found in osteomalacia by the calcium
infusion test (Nordin and Fraser, 1956; Kehayoglou,
The highest urinary outputs of infused radiocalcium
were found in two patients with normal calcium
absorption. In two of the other patients there was
histological evidence of osteoporosis and in the
remainder iliac crest biopsy was normal. In view of
the bone pain it is possible that there could have been
metabolic bone disease at other sites.

The subjective relief of bone pain was similar
to that reported by Pak et al (1969) in six patients
with idiopathic osteoporosis. Sekel (1973) also
reported the relief of bone pain following a course
of calcium infusions in patients with Paget's disease
of bone and noted 'striking relief from pain after
the third day of infusion and relief has persisted
sixteen weeks after the infusion ceased'. In contrast
to the findings of Pak et al (1969), after the course
of calcium infusions we found no changes in
calcium retention or in bone biopsies, with one
exception (case 10). Their studies, however, were
performed on patients with idiopathic osteoporosis.

The mechanism of the effectiveness of intravenous
calcium infusion therapy in the relief of bone pain
in the group of patients with primary biliary cirrhosis
The relief of bone pain in primary biliary cirrhosis with calcium infusions

Comparison of three isotopic methods for the study of calcium absorption. Gut, 10, 590-597.


References