Effect of salmon calcitonin on cardiac output, oxygen transport and bone turnover in patients with Paget's disease

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Summary
1. Twelve patients with symptomatic Paget's disease were studied before starting treatment with salmon calcitonin (12.5 μg) subcutaneously twice daily. Eleven of them were studied again after 3 months on this therapy.
2. Although pretreatment values for urinary total hydroxyproline excretion and cardiac output were considerably increased in some patients, there was no correlation between these two variables in the group as a whole.
3. Treatment resulted in a striking reduction in disease activity; the mean urinary hydroxyproline decreased 67%.
4. There was, however, no significant fall in cardiac output or change in oxygen transport during treatment.
5. Of the eight patients with bone pain who received treatment, five claimed complete pain relief.

Key words: bone, calcitonin, cardiac output, oxygen, Paget's disease.

Introduction
In active Paget's disease, there is an increase in bone blood flow (Edholm, Howarth & McMichael, 1945). When the disease process is extensive, there may be an increase in cardiac output (Howarth, 1953) associated with a fall in peripheral resistance thought to result from dilatation of the vessels forming the capillary bed in bone (Rutishauser, Veyrat & Rouiller, 1954). Arteriovenous anastomoses have not been identified (Rhodes, Greyson, Hamilton, White, Giargiana & Wagner, 1972).

The abnormally raised turnover of the bone in Paget's disease can be reduced by long-term treatment with calcitonin (Woodhouse, Reiner, Bordier, Kalu, Fisher, Foster, Joplin & MacIntyre, 1971; Singer, Keutmann, Neer, Potts & Krane, 1972; De Rose, Avramidies, Baker & Wallach, 1972; Woodhouse, 1974), which in addition may sometimes produce radiological healing of the disease (Doyle, Pennock, Greenberg, Joplin & MacIntyre, 1974). Relief of bone pain has also been claimed by many patients. Such treatment therefore might also lower the cardiac output. This possibility has been investigated in a group of patients before and after 3 months' treatment with salmon calcitonin.

Patients
Informed consent was obtained for this study from the twelve patients who had been consecutively referred to the Medical Unit for further management. All had Paget's disease of widely ranging clinical and biochemical severity. Their details are shown in Table 1. Eight patients had bone pain but in only four cases with affected peripheral bones was this judged to be due to the Paget's disease alone. The others had degenerative joint disease as well. Three patients had headache (E.L., E.W. and A.R.) and one patient (F.T.) had progressive deformity and deafness. Follow-up studies are not available in patient E.W., who refused further treatment after 2 months. Cardiopulmonary studies were not repeated in patients E.L. and A.R.
Methods and materials

The patients were studied on a self-selected, low-gelatin ward diet. At least four 24 h urine collections were obtained before starting calcitonin and during the 3 months' follow-up admission on treatment.

The cardiac output and gas-exchange studies were made with the subjects resting on a couch approximately 2 h after a light breakfast and half an hour after a plastic cannula was inserted into the brachial artery under local anaesthesia. No premedication was given. The cardiac output was measured with the indicator-dilution technique. A bolus of iodinated (125I-labelled) human serum albumin B.P. (The Radiochemical Centre; 3 μCi/ml) was injected by way of a venous catheter positioned in the median vein and followed by a flush of 150 mmol/l sodium chloride (20 ml). Serial blood samples were collected in an automated fraction collector (Crosbie & Wyatt, 1971) from the brachial artery catheter. The radioactive counts in each tube were measured in an automated gamma spectrometer together with standards made from dilutions of the injected solution. Indicator dilution curves were then constructed from the raw data, a Fortran Program and CDC 1800 computer being used to calculate the cardiac output value (Crosbie, Clark & Banks, 1973).

Expired gas was collected in a 200L Tissot spirometer and the mixed expired oxygen concentration measured with a Servomex paramagnetic analyser; the carbon dioxide concentration was measured with a Capnograph infrared analyser. The arterial blood gas tensions and pH were measured with a Corning-EEL electrode system and the arterial saturation was calculated from the PaO₂ and pH. The haemoglobin concentration was measured in a Coulter model S analyser. The oxygen uptake was calculated from the expired gas collection. The mean venous oxygen saturation was calculated from the oxygen uptake, cardiac output, haemoglobin concentration and arterial oxygen content. Urinary hydroxyproline concentrations were measured by the method of Kivirikko, Laitinen & Prockop (1967). Body surface area of patients was calculated from height and weight.

Synthetic salmon calcitonin solution (Armour Pharmaceutical Co. Ltd) was supplied in 2 ml vials containing 50 μg/ml calcitonin (200 MRC units/ml). Each patient received 12.5 μg (50 MRC units) of salmon calcitonin subcutaneously twice daily by self-administration for 3 months. Five patients noticed a feeling of warmth in the face and hands lasting from 15 to 60 min after an injection. One patient felt slightly nauseated at the onset of treatment but this lasted only a week. There were no other systemic or local reactions.

Results

Complete relief of bone pain and loss of bone tenderness was reported by all four patients with diseased peripheral bones (J.C., G.F., C.L. and M.B.). Clinically, the skin overlying affected tibiae became cooler and more resembled that on the normal side during treatment (J.C., G.F. and C.L.). One other patient (I.W.) with multiple compression fractures of the vertebrae, experienced almost total relief of her severe backache with a corresponding improvement in her mobility. There was no demonstrable radiological improvement in affected bones in any of the nine patients followed over this 3 month treatment period.

There was no correlation between the pretreatment disease activity, in terms of urinary hydroxyproline excretion, and the resting cardiac output (r = 0.43, P > 0.1). Urinary hydroxyproline excretion was strikingly reduced by treatment (Table 1); the mean fall was 67%.

There was a wide range in the resting cardiac output before (2.7-11.9; mean 5.5 l min⁻¹ m⁻²) and during (2.4-6.9; mean 4.9 l min⁻¹ m⁻²) treatment. The difference between the two groups was not statistically significant at the 5% level by the paired t-test. The oxygen uptake was within the expected normal range in all except one subject (W.R.). The arteriovenous oxygen content difference was inversely related to the cardiac output, indicating that tissue oxygen demand was normal. There was little change in any of these parameters during treatment except in patients I.W. and J.C. (Table 1).

Discussion

This study confirms the presence of an increased resting cardiac output in some patients with Paget's disease (Edholm et al., 1945; Howarth, 1953); ten of our twelve patients had values of 2.9 l min⁻¹ m⁻² or more. There was, however, no correlation between these values and the activity of the disease process assessed by measurement of the urinary total hydroxyproline excretion.

Treatment with salmon calcitonin produced a
Calcitonin in Paget's disease

Urinary hydroxyproline values represent the mean of at least four 24 h collections for each patient. The oxygen uptake, cardiac output and arteriovenous oxygen content difference were measured in the resting state. Normal values are expressed as range or as mean value ±so. Sources are: hydroxyproline excretion, this study; oxygen uptake, Grameth, Jonsson & Strandell (1964); cardiac output, Bradfordbrener, Landowne & Shock (1955); arteriovenous (a-v) oxygen difference, Reeves, Grover, Filley & Blount (1961).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Hydroxyproline (mmol/day)</th>
<th>Oxygen uptake (ml/min)</th>
<th>Cardiac index (l min⁻¹ m⁻²)</th>
<th>Oxygen a-v difference (ml/l)</th>
<th>Surface area (m²)</th>
<th>Hydroxyproline (mmol/day)</th>
<th>Oxygen uptake (ml/min)</th>
<th>Cardiac index (l min⁻¹ m⁻²)</th>
<th>Oxygen a-v difference (ml/l)</th>
<th>Surface area (m²)</th>
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<tbody>
<tr>
<td>C.L.</td>
<td>F</td>
<td>57</td>
<td>0.37</td>
<td>122</td>
<td>6.0</td>
<td>17</td>
<td>1.55</td>
<td>0.32</td>
<td>160</td>
<td>2.8</td>
<td>49</td>
<td>1.56</td>
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<tr>
<td>J.G.</td>
<td>M</td>
<td>71</td>
<td>1.38</td>
<td>168</td>
<td>3.5</td>
<td>36</td>
<td>1.71</td>
<td>0.53</td>
<td>186</td>
<td>5.3</td>
<td>27</td>
<td>1.71</td>
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<tr>
<td>G.F.</td>
<td>F</td>
<td>68</td>
<td>0.86</td>
<td>227</td>
<td>2.8</td>
<td>66</td>
<td>1.63</td>
<td>0.28</td>
<td>227</td>
<td>2.4</td>
<td>74</td>
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<tr>
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<td>2.70</td>
<td>117</td>
<td>3.1</td>
<td>30</td>
<td>1.78</td>
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<td>244</td>
<td>6.9</td>
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<td>M.B.</td>
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<td>187</td>
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<td>1.45</td>
<td>0.21</td>
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<td>47</td>
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<td>52</td>
<td>3.56</td>
<td>135</td>
<td>11.9</td>
<td>11</td>
<td>1.26</td>
<td>1.79</td>
<td>158</td>
<td>5.2</td>
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<td>A.C.</td>
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<td>0.80</td>
<td>206</td>
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<td>43</td>
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<td>3.3</td>
<td>44</td>
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</tr>
<tr>
<td>F.T.</td>
<td>M</td>
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<td>6.88</td>
<td>214</td>
<td>3.6</td>
<td>46</td>
<td>1.66</td>
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<td>188</td>
<td>4.0</td>
<td>37</td>
<td>1.66</td>
</tr>
<tr>
<td>W.R.</td>
<td>M</td>
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<td>1.45</td>
<td>294</td>
<td>6.2</td>
<td>32</td>
<td>1.90</td>
<td>0.63</td>
<td>390</td>
<td>5.7</td>
<td>46</td>
<td>1.90</td>
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<tr>
<td>E.L.</td>
<td>M</td>
<td>63</td>
<td>2.08</td>
<td>217</td>
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<td>47</td>
<td>1.37</td>
<td>1.36</td>
<td>108</td>
<td>4.2</td>
<td>38</td>
<td>1.36</td>
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<tr>
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<td>1.15</td>
<td>200</td>
<td>3.0</td>
<td>54</td>
<td>1.62</td>
<td>0.50</td>
<td>109</td>
<td>4.2</td>
<td>40</td>
<td>1.62</td>
</tr>
<tr>
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<td>10.2</td>
<td>161</td>
<td>7.4</td>
<td>20</td>
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<td>1.37</td>
<td>0.50</td>
<td>109</td>
<td>4.2</td>
<td>40</td>
<td>1.62</td>
</tr>
</tbody>
</table>

Normal range: 0.11–0.34 255±34 2.58±0.15 38.4±6.3

striking reduction in bone turnover, expressed as hydroxyproline excretion, in all the patients. In spite of this, there was no fall in cardiac output in the group as a whole. This was surprising, as there had been a clinically obvious reduction in skin temperature in the three patients with diseased tibiae. Possibly, periosteal blood flow is the first to fall and a similar change in the vascular channels of the underlying bone tissue requires longer periods of treatment. It is also possible that the abnormal bone vascularity of Paget’s disease is an integral part of the pathological process rather than a secondary response to abnormal bone cell activity and altered bone architecture. In this situation, treatment with calcitonin might reduce bone turnover without reducing the abnormal bone vascularity. As the cardiac output probably returns to within the normal range when the disease process burns out (Edholm & Howarth, 1953), a repeat study after a year or more’s treatment with calcitonin should answer this question.

Using a technique similar to the one used in this study, McNeely & Gravallesse (1954) reported that a second estimate of cardiac output was within 25% of the initial value in 95% of instances. With this criterion, we observed no change in cardiac output in five patients, a fall in two and an increase in the remaining two, after 3 months’ treatment with salmon calcitonin. Patient C.L. was recovering from a lower respiratory tract infection and had residual consolidation on the chest X-ray at the time of her first measurement. This may have accounted for the abnormally high initial value as her Paget’s disease was localized to the lower half of the right tibia and her cardiac output subsequently returned to within the normal range. Treatment with calcitonin may have produced the fall in cardiac output in patient L.W., who had radiologically extensive and initially biochemically active disease. We have no explanation for the rise in cardiac output that occurred during treatment in two patients (J.C. and J.G.), except that one of them (J.C.) had become anaemic (haemoglobin 9.5 g/100 ml) due to bleeding haemorrhoids. These results conflict with those of Goldsmith, Arnaud & Benson (1971), who reported a fall in cardiac output within the first 2–3 months in patients receiving porcine calcitonin. These changes were small, however, and with the exception of one patient were not sustained during long-term treatment.

As previously noted during calcitonin treatment, relief of bone pain has been a striking feature and occurred in some of the patients reported here. Complete disappearance of the pain was claimed by all the four patients with affected peripheral bones (one femur and three tibiae) and considerable relief by one patient with gross Paget’s disease, multiple vertebral fractures, severe headache and
back pain. The other three patients did not improve and all of these had either low back pain or hip pain, which was associated with degenerative joint disease as well. These observations were not controlled but taken in conjunction with the simultaneous biochemical improvement and loss of bone tenderness suggest that calcitonin is sometimes very valuable in the management of painful Paget's disease.

Acknowledgments

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References


