A controlled trial of the effect of topical glyceryl trinitrate on skin blood flow and skin elasticity in scleroderma

It has been suggested that in systemic sclerosis (SSc) the primary fault is in the microcirculation.\(^1\) If this were so, then topical glyceryl trinitrate (GTN) might favourably influence skin blood flow and elasticity in areas of temperature skin change.

Ten patients (three men, seven women; median age 48 years, range 24–70) fulfilling the American Rheumatism Association criteria for SSc\(^2\) were recruited into a double-blind placebo trial. All had had forearm skin involvement and the median disease duration was 2.5 years, range seven months to 18 years. The extent of forearm skin involvement varied between patients. Many had skin thickening (involved, but skin could be pinched) and only one had classical ‘hidebound’ skin.

For four weeks each patient applied topical GTN (2%) three times daily to a designated area of antecubital fossa, and a lanolin-based placebo ointment to the corresponding area of the other. Careful instructions and a demonstration of how much ointment to apply were given and the patient wore gloves to minimize absorption from other sites. Elasticity (using a Cutech Extensometer), skin blood flow (by the laser Doppler technique using a Perimed PF3 instrument) and skin thickness (using a Heimann KT41 Brometer) were measured at both sites at baseline, one hour post initial ointment application, and after two and then four weeks of treatment. The third and fourth assessments (at two and four weeks respectively) were made three hours after ointment application. Coefficients of variance (median and range) were 7.6% (1.7–22) for elasticity measurements, 42% (6.6–56%) for laser Doppler readings and 2% (0.6–4) for bolometry.

Baseline and post-treatment results within each group (GTN and placebo treated) were compared using a Signed rank test. Changes from baseline (one site was compared between groups using a Mann-Whitney U-test).

Two patients withdrew from the study because of adverse effects of the trial treatment. One withdrew after three days, complaining of a stinging sensation in both arms following the application of the trial treatment. The other withdrew after the two week visit, complaining of discomfort in what proved to be the arm treated with GTN, and headaches. Data were therefore only available from these patients for the first two and three assessments respectively. Otherwise all the patients completed all assessments, with the exception of one patient, who, due to computer malfunction, did not have a laser Doppler measurement at her second (one hour post-first application) assessment.

Results for elasticity, laser Doppler and bolometry assessments are shown in the table. With the exception of a statistically significant difference between the bolometry readings of the GTN treated group at baseline and one hour, there were no significant changes over time in any of the three parameters measured in either the GTN or placebo treated forearms. Nor were there any significant differences in these changes between the two groups.

<table>
<thead>
<tr>
<th>Elasticity, blood flow and temperature measurements in topical GTN and placebo-treated forearms</th>
<th>Baseline (n = 10)</th>
<th>1 hour (n = 10)</th>
<th>2 weeks (n = 9)</th>
<th>4 weeks (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elasticity</strong></td>
<td></td>
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<tr>
<td>Topical GTN</td>
<td>635-6 (332-594)</td>
<td>554-5 (354-484)</td>
<td>561-1 (251-1291)</td>
<td>554-9 (357-823)</td>
</tr>
<tr>
<td>Lanolin</td>
<td>540-9 (271-928)</td>
<td>538-5 (196-992)</td>
<td>532-3 (264-719)</td>
<td>488-8 (218-927)</td>
</tr>
<tr>
<td><strong>Laser Doppler</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Topical GTN</td>
<td>5-8 (3-1.8-8)</td>
<td>10-3 (1-4-37-9)</td>
<td>10-9 (7-4-12-7)</td>
<td>9-5 (5-4-22-1)</td>
</tr>
<tr>
<td>Lanolin</td>
<td>7-6 (3-1.23-6)</td>
<td>7-7 (2-3-13-2)</td>
<td>8-7 (4-8-22)</td>
<td>8-0 (2-5-13-0)</td>
</tr>
<tr>
<td><strong>Bolometry</strong></td>
<td></td>
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<tr>
<td>Topical GTN</td>
<td>31-4 (30-36-33)</td>
<td>32-9 (30-33-4)</td>
<td>32-9 (29-32-37)</td>
<td>31-6 (30-1-2-7)</td>
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<tr>
<td>Lanolin</td>
<td>31-9 (30-1-33-7)</td>
<td>32-9 (30-3-33-0)</td>
<td>32-9 (29-6-33-9)</td>
<td>31-9 (29-2-3-1)</td>
</tr>
</tbody>
</table>

* p < 0.05 versus baseline  \( z \) test

Results are median (range)

Regarding ointment utilisation, this varied considerably between patients but there was a tendency for patients to use similar amounts on each arm. Similar amounts of GTN and placebo ointments were used by the nine patients completing the first two weeks period as follows: median amount of GTN consumed 4.6 g, range 1.4 to 8.1 g, median amount of placebo ointment used 3.2 g, range 1 to 7.3 g.

The application of topical GTN over a four week period therefore had no effect on skin elasticity or skin blood flow detectable by the methods used. Possible explanations for these negative findings include the importance of factors other than the microcirculation in the pathogenesis of SSc, the short time interval studied, and dermal blood vessel wall changes which were already irreversible in this patient group at the time of study.

It has been suggested that topical GTN is helpful in the management of secondary Raynaud’s, in combination with oral methyldopa or guanethidine.\(^3\) Coppeck et al demonstrated a reduction in cold-induced vasospasm after topical GTN in patients with secondary Raynaud’s. In our study, however, did not examine the circulation of the hand but skin thickening and skin blood flow of the forearm.

Any benefit from topically applied GTN is likely to arise from a combination of local and systemic effects. Our study was useful in demonstrating that in most patients the treatment was well tolerated, and also that ointment application (either placebo or GTN) did not in itself distort skin elasticity. Further studies should be longer term and include patients with early disease in whom dermal microvascular changes are likely still to be reversible.

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**Osteoporosis and Ehlers-Danlos syndrome**

The changes in bone mineral content of patients with Ehlers-Danlos syndrome (EDS) are still not wholly defined. Although well described in diseases of the same group (ostogenesis imperfecta, homocystinuria), osteoporosis is seldom consistently referred to in association with EDS.\(^4\) Prokop suggests that the mutations altering the sequence of the N-terminal extremity of the procollagen, as is the case with the EDS groups of EDS, would not cause a diminution of the bone mass.\(^2\) However, some studies appear to indicate that in EDS there is an alteration in the normal bone metabolism, finding an increase in the frequency of vertebral fractures and ultrastructural changes in the collagen fibrils. It also seems that there is a lower absorption of tetracycline in the bone tissue of patients with type I EDS.\(^7\)

We recently assessed, using dual energy x ray absorptiometry (Hologic QDR1000), four of six patients with type I EDS observed in the outpatients clinic of the Rheumatology Unit of the Hospital Militar Principal (the two patients not included were children aged four and seven years), three male and one female patient, with ages ranging from 16–25 years. None of the patients presented other significant factors for low bone mass and none had clinical or radiological evidence of vertebral crush fractures. Data obtained were compared to our reference data, composed of healthy Portuguese students, male and female (military and young female workers of military units). Each year of life of our reference group is composed of 30 individuals of each sex (ex: 16 y—30 male and 30 female). The BMD values found proved to be, at the level of the lumbar spine, persistently below 1 standard deviation of the average for sex and age. These differences were minimal or non existent for the femur neck (see table).

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Letters to the editor/Matters arising

The data we obtained suggested that the changes in the bone mineral content in EDS patients, although less intense than in other hereditary collagen diseases, are also present. Our study also suggests that this reduction in bone mass only affects predominantly trabecular bone. Subsequent studies involving greater numbers of patients and a clarification of the biochemical and genetic mechanisms involved in type I EDS should further clarify this subject.

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MATTERS ARISING

G-CSF in gold-induced aplastic anaemia

A letter from MacDonald et al1 reported the case of a 55 year old woman with psoriatic arthritis who developed aplastic anaemia after gold treatment, and was reported to have a less than therapeutic response to filgrastim (G-CSF, Neupogen) therapy. Approximately 30 days after the gold treatment was discontinued, a bone marrow aspirate and biopsy revealed severe aplasia. She was then treated with filgrastim 1.5 mcg/kg on alternate days for three days, then daily for an additional 10 days.

The idiosyncratic myelotoxicity of gold therapy has been well documented and filgrastim (r-metHuG-CSF) demonstrating the therapeutic dose range for these conditions has not been determined, the standard dose of filgrastim for chemotherapy induced neutropenia has been 5 mcg/kg/day.

Before approval by the Food and Drug Administration, Amgen Inc provided filgrastim to patients with non-cytotoxic drug-induced agranulocytosis in a compassionate use protocol. One of these patients was a 20 year old woman who had developed agranulocytosis after five weeks of gold therapy. For two weeks after the discontinuation of gold treatment the patient had an absolute neutrophil count (ANC) of 0/mm, and then received filgrastim 10 mcg/kg/day, attaining an ANC of 5100/mm after four days of filgrastim treatment. Although this was not a controlled clinical trial, this experience demonstrates the activity of filgrastim in enhancing myeloid recovery.2 The patient described by MacDonald et al may have had an improved response with a higher dose of filgrastim.

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Brother and sister with myeloperoxidase associated autoimmune disease

We read with interest the recent article by Murphy et al1 describing two sisters with vasculitis associated with antineutrophil cytoplasmic autoantibodies (ANCA). We report a brother and sister with autoimmune disease and circulating antibodies directed against myeloperoxidase.

The brother, aged 77 years, presented with arthralgia, thinning of the skin, and a gradually deteriorating renal function. A renal biopsy revealed extracapillary focal segmental glomerulonephritis and active vasculitis in a blood vessel. Antinuclear antibodies (ANA), anti-dsDNA, IgM rheumatoid factor and LE-cell test were negative. ANCA were positive with a perinuclear pattern of staining at a titre of 1/64. The antibodies were directed against myeloperoxidase. Treatment with cyclophosphamide and steroid resulted in rapid recovery of renal function and the immuno-suppressive drugs were tapered. The patient died two years later of myocardial infarction.

The sister presented at the age of 61 with a bilateral pleuritis sicca and arthralgia. ANCA were negative, anti-dsDNA (Farr assay) were negative, LE cells were positive (class 5C), IgM rheumatoid factor was negative. ANCA were repeatedly positive with a perinuclear pattern of staining (titre 1/512). ELISA revealed antibodies against myeloperoxidase. She was initially treated with steroids but subsequently needed azathioprine to control recurrent pleuritis sicca and arthralgia. Two years after the first presentation she still requires azathioprine. There has been no evidence of renal disease.

Although the clinical presentation of disease in both siblings differed widely—elder sister presented with an idiopathic extracapillary proliferative glomerulonephritis whereas the sister suffered from a lupus like disease—both were found to have circulating antibodies directed against myeloperoxidase. Apart from the recent report in the Annals,3 there has been another communication on ANCA positive vasculitis in siblings: Ten Hacken et al reported Wegener’s granulomatosis in a mother and daughter, associated with anti-myeloperoxidase antibodies in the former and c-ANCA in the latter.4 We agree with Murphy et al, that a relatively rare disease like ANCA associated vasculitis within one family suggests a role for genetic factors, although environmental factors may also play a role. Whether family members from patients with ANCA associated disease have an increased prevalence of circulating ANCA, and if this is associated with an increased risk for developing connective tissue disease, remains to be clarified.

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Table

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (years)</th>
<th>Lumbar (L1–L4)</th>
<th>Femur Neck</th>
<th>Ward’s</th>
<th>BMD</th>
<th>Z-score</th>
<th>BMD</th>
<th>Z-score</th>
<th>BMD</th>
<th>Z-score</th>
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<tbody>
<tr>
<td>M</td>
<td>16</td>
<td>0.760</td>
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<tr>
<td>M</td>
<td>21</td>
<td>0.867</td>
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<tr>
<td>F</td>
<td>25</td>
<td>0.885</td>
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<tr>
<td>F</td>
<td>25</td>
<td>0.915</td>
<td>-1.63</td>
<td>0.945</td>
<td>-0.09</td>
<td>0.766</td>
<td>-0.25</td>
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</table>

BMD = Bone mineral density (g/cm²)

M = Male
F = Female

<table>
<thead>
<tr>
<th>Patient</th>
<th>ANCA</th>
<th>ANA</th>
<th>LE</th>
<th>Anti-dsDNA</th>
<th>Anti-cardiolipin</th>
<th>Anti-phospholipid</th>
<th>Anti-Thy-1</th>
<th>Anti-SSB</th>
<th>Anti-SSA</th>
<th>Anti-GBM</th>
<th>Anti-RNP</th>
<th>Anti-Sm</th>
<th>Anti-Jo-1</th>
<th>Anti-Scl-70</th>
<th>Anti-dsDNA</th>
<th>Anti-RNP</th>
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</tbody>
</table>

The table lists the patient’s medical history, including ANCA and ANA status, and other autoantibodies.

213