An Experimentally Controlled Evaluation of the Effect of Inositol Nicotinate upon the Digital Blood Flow in Patients with Raynaud's Phenomenon

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The vaso-active effects of inositol nicotinate (Hexopal®) were investigated in thirty patients with primary and secondary Raynaud's phenomenon using several non-invasive experimental techniques under controlled conditions. The earlier formed impression that this drug requires a prolonged 'build-up' period was confirmed. Recording the time required to induce Raynaud's phenomenon as well as assessments of total and nutrient digital blood flow showed significant beneficial therapeutic effects upon the skin's microcirculation by inositol nicotinate.

This study suggests that the therapeutic effect of this drug is not merely due to vasodilation but that other mechanisms such as enhanced fibrinolysis and lowering of serum lipids may play a significant part in its overall effect.

Smokers responded slower than non-smokers, but even elderly patients with longstanding vasospastic disease showed measurably improved digital circulation. Unlike some other drugs in this field inositol nicotinate was found to be effective orally and to be devoid of unwanted side-effects. However, in the majority of patients it failed to abolish their increased vascular spasm although it diminished it significantly in most. It appears to be a safe and well tolerated drug, which, together with other symptomatic measures, merits to be used in the management of vasospastic disease of the extremities even in the presence of partial obliteration of the microcirculation.

Introduction

Vasospastic conditions of fingers and toes such as acrocyanosis, pernio sis and Raynaud's phenomenon are common in this country. Raynaud's phenomenon starting at adolescence is nearly always 'benign' and, unlike the appearance of this clinical manifestation later in life, not associated with an underlying obliterative vascular disease such as systemic sclerosis, lupus erythematosus or dermatomyositis. Whether or not an associated or underlying cause for digital vasospastic disease can be identified, drugs giving effective symptomatic relief are required in their management.

There is an embarrassing paucity of
published reports of well-controlled evaluations of such orally administered drugs which are widely prescribed because of their manufacturers' claims, the need for effective vasoactive agents and placebo effects.

Since derivatives of nicotinic acid, devoid of the unwanted side-effects of their parent substance, have been shown to be of therapeutic benefit, an experimentally controlled evaluation of inositol nicotinate (Hexopal®) was undertaken using several instrumental methods assessing its effect upon the digital circulation in patients with Raynaud's phenomenon.

An earlier study based on a double-blind, randomized, within-patient crossover design, with a single-blind wash-out period between each of 2-week treatment periods had failed to show statistically significant instrumentally measurable differences between placebo and inositol nicotinate, 1 g thrice daily, using several complementary instrumental parameters under controlled experimental conditions (Holti 1978).

Clinical observation of over 100 patients taking inositol nicotinate in higher doses for several months during the cold season had indicated that a treatment period longer than 2 weeks may be required before significant changes can be demonstrated with the tests used during the earlier study. It was, therefore, decided to undertake a single-blind study during which patients would take the placebo for 4 weeks, followed by three 4-week test periods during which they would take inositol nicotinate in the dose of 1 g four times daily.

The justification for this unconventional trial design was not only the clinical impression that this drug required a prolonged 'build-up' period before showing beneficial therapeutic effects, but also considerable published evidence that esterified nicotinic acid derivatives are not merely short-acting vasodilators but that their vaso-active effects include enhanced fibrinolysis, lowering of increased serum cholesterol, fibrinogen and free fatty acid levels, and diminished platelet stickiness (Kappert 1961, Sommer 1965, Benaim & Dewar 1975). In view of these considerations a within-patient placebo-drug crossover design is not suitable for the pharmacological evaluation of such drugs since patients starting their trial with an effective vaso-active drug would show beneficial effects, such as the dissolving of not yet organized microthrombi, 'carried-over' through the intervening 'wash-out' period into the placebo treatment stage of a double-blind 'within-patient' crossover trial.

**Trial Design, Patients and Experimental Methods**

**Trial Design**

The study was single-blind, of 16 weeks duration, with an initial 4 weeks' wash-out period followed by a 12-week period during which patients took daily 4 g of inositol nicotinate in divided doses. Patients were tested on entering the trial and at the end of each of the four 4-week trial periods to undergo biometric tests, to have blood taken for the estimation of serum lipids, fibrinogen, measurement of plasma viscosity, liver function tests and full blood counts. They received their 4-week supplies of tablets at each visit without knowing whether they contained a pharmacologically active substance or a placebo.

**Patients**

Thirty patients entered and completed this trial, twenty-six females and four males.

Their ages ranged from 25–68 years.

In fourteen patients extensive investigations had not produced any evidence of an underlying obliterative vascular disease, whereas in sixteen cases evidence of the presence of systemic sclerosis (5), subacute lupus erythematosus (5) or of arteriosclerosis obliterans (6) had been found. The former group was diagnosed as suffering from 'primary' and the latter from 'secondary' Raynaud's phenomenon.

All patients had been under the surveillance of the same investigator for several years, had given their informed consent to participate in the evaluation of this drug and were known as reliable takers of medication prescribed for them and dependable attenders for the relatively long testing procedures. The severity of their Raynaud's phenomenon ranged from mild to moderately severe. Patients with severe digital ulceration were not included.
Exclusion criteria:
(1) postural hypotension,
(2) concurrent illness,
(3) pregnancy,
(4) impaired renal or hepatic function,
(5) prescribed medication known to influence blood lipids, serum viscosity or cardiac function.

Patients were asked to avoid self-medication with aspirin-containing preparations (e.g. Alka-Seltzer, Beecham's powders, etc.) and to abstain from smoking. They were requested to notify the investigator of any intercurrent illness and medication prescribed for them during the trial by their family doctors or hospital physicians.

Table 1

<table>
<thead>
<tr>
<th>Raynaud's phenomenon</th>
<th>Age (years)</th>
<th>25–30</th>
<th>31–40</th>
<th>41–50</th>
<th>51–60</th>
<th>61–70</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30</td>
</tr>
</tbody>
</table>

Table 2

Duration of Raynaud's phenomenon

<table>
<thead>
<tr>
<th>Raynaud's phenomenon</th>
<th>Duration (years)</th>
<th>1–10</th>
<th>11–20</th>
<th>21–30</th>
<th>31–40</th>
<th>40+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td>2</td>
<td>9</td>
<td>2</td>
<td>1</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td>8</td>
<td>5</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>10</td>
<td>14</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>30</td>
</tr>
</tbody>
</table>

Table 3

Smoking habits

<table>
<thead>
<tr>
<th>Raynaud's phenomenon</th>
<th>Smoker</th>
<th>Light</th>
<th>Heavy</th>
<th>Non-smoker</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td>3</td>
<td>3</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td>6</td>
<td>3</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td>9</td>
<td>6</td>
<td>15</td>
<td>30</td>
</tr>
</tbody>
</table>
Patients' Characteristics
These are shown in Tables 1, 2 and 3.

Environmental temperature
The trial was commenced during the spring and continued until the early summer months. It was originally planned to carry it out during the winter, but in spite of the time of year unusually cold and humid weather created suitable environmental conditions for patients' subjective assessment of their treatment and for some of the testing procedures. In order to standardize testing conditions all patients were examined and tested each time either between 0800 and 0930 hrs, or after 1630 hrs. Each testing session lasted between 1 and 2 hours.

Methods of objective assessment
(1) At each visit the following data were entered on the patients' records:
(a) weight,
(b) blood pressure, supine after a standard rest period,
(c) state of peripheral pulses,
(d) clinical evidence of digital ischaemia,
(e) smoking habits,
(f) details of any intercurrent indisposition and medication.

(2) Blood tests
Venous blood was withdrawn for the estimation of:
(a) full blood counts, including estimation of the differential white cell and platelet counts,
(b) liver function tests,
(c) estimation of blood viscosity (using the Coulter apparatus).

(3) Induction of Raynaud's phenomenon
Raynaud's phenomenon was induced (if not present on arrival in the laboratory) by the patient holding a metal tray containing ice cubes (as used in domestic refrigerators). It was found that this method gave consistent results only if the patient's oral temperature was not higher than 36°C. For this reason body-cooling (in a cold room or by immersing their forearms in iced water for 15–20 minutes) was required on relatively warm days.

The time required to induce blanching of finger tips was recorded.

(4) Assessments of digital blood flow
(a) Total digital skin blood flow was assessed by applying to each fingertip a rapidly recording copper-tellurite-copper thermopile (Holti 1955).
(b) Nutrient skin blood flow was estimated using a recently modified non-invasive thermal clearance probe (Holti & Mitchell 1978).

Explanatory note concerning this technique
Only blood in the upper (papillary) dermis at a depth of 1·5–2·0 mm from the surface of the horny layer constitutes the nutrient flow to the avascular epidermis and, if insufficient, determines the appearance of ischaemic skin lesions.

The non-invasive thermal clearance technique has many advantages over measurements based on the disappearance rate of intradermally injected radio-pharmaceuticals. The thermal clearance probe method estimates the rate of removal of heat by the upper dermal blood flow from a heated copper disc at the centre of its lower surface, which is applied to the skin, as compared to an unheated copper annulus at its periphery. Six copper-constantan thermocouples are soldered in series to an equal number of segments of the heated central disc and the unheated peripheral annulus, giving a differential temperature sensitivity of 240 microvolts °C⁻¹.

When interpreting readings with this apparatus it is essential to realize that a high reading indicates a low rate of thermal clearance by a sluggish bloodflow while a fast flow will raise the temperature of the unheated annulus and the thermo-electric current generated at the six thermal junctions will be correspondingly smaller. The thermal clearance rate is expressed as ΔT°C. The lower its numerical value the higher is the nutrient skin blood flow.
(5) Induction of digital hyperaemia

(a) Maximal peripheral vasodilation was then induced by immersing the patients' hands and forearms in hot water (43°C–45°C) until their oral temperature had reached at least 37.5°C. At that stage their fingertip temperatures and thermal clearance rates were again recorded after an interval of 5 minutes had allowed the disappearance of the direct heating effect of the warm water upon the horny layer.

(b) At that stage the vascular tone of the digital circulation was tested by trying to induce reactive hyperaemia. The circulation to one hand was blocked for 5 minutes using an inflatable cuff at supra-systolic pressure applied to the upper arm. The hyperaemic response in the hand after the cuff had been released was measured in the fingertips using skin thermometry and the thermal clearance rate. The speed of onset of reactive hyperaemia, its peak height, and its duration were recorded. If a transient ‘peak’ increase in the rate of blood flow did not occur within 90 seconds of the cuff being released, patients were considered not to have responded with reactive hyperaemia to their experimentally induced ischaemia. The absence of significant reactive hyperaemia is a feature of the increased vascular tone in individuals subject to attacks of Raynaud’s phenomenon. It reflects their high peripheral vascular tone. For this reason this test was done after patients had been warmed and when their skin arterioles and venules were not in spasm, yet not maximally dilated.

(6) Miscellaneous data

(a) At each testing session the external and laboratory temperatures were recorded.

(b) Patients were asked about any change in their smoking habits.

(c) They were asked about their subjective assessment of their treatment and about any side-effects.

(d) They were given a fresh 4-week supply of their tablets except after the last (5th) testing session.

Individual record cards were completed for every patient at the end of each testing session and these were not scrutinized until the study had been completed.

Results

The thirty patients who entered the trial completed it.

This study provided a large number of data in the form of clinical observations and instrumental readings suitable for statistical analyses. The following information was evaluated:

(1) Fingertip temperatures on arrival (from a cold ambience).

(2) Thermal clearance rates on arrival.

(3) Time required to induce Raynaud’s phenomenon.

(4) Maximal fingertip temperature after inducing hyperthermia.

(5) Maximal thermal clearance rates after inducing hyperthermia.

(6) Speed of onset of reactive hyperaemia (if it occurred), its peak temperature and its peak thermal clearance rates.

(7) Differences between the maximal skin temperatures and thermal clearance rates obtained during hyperaemia and the readings obtained during arterial occlusion.

1. Finger temperatures

Although the patients had been grouped as suffering from primary and secondary Raynaud’s phenomenon, in the statistical analysis of the data they could be treated as one group because there were not any significant differences between the two groups for any readings.

A t-test was carried out comparing the means at Weeks 4, 8 and 12 with the mean at Week 0.

There were significant differences at the 99% level (p<0.01) at Weeks 4, 8 and 12 for the ‘on arrival’ readings. There were no significant differences in the ‘after heating’ readings.

Comment: The ‘after heating’ readings (Table 4) indicate that none of the patients suffered from significant obliterative vascular changes
of their finger tips' microcirculation, whereas they clearly had vasospastic disease.

It was noted that the 'on arrival' readings (Table 5) tended to correlate with the outside temperature. However, after allowing for this effect the weeks which had given 'significant' results previously still gave significant t-values.

2. Thermal clearance
Table 6 sets out the mean values of readings obtained over the fingertips of both hands 'on arrival' in the laboratory and after maximal vasodilation had been induced.

Paired t-tests were carried out to compare the means of both the 'on arrival' and 'after heating' readings at Weeks 4, 8 and 12 with those at Week 0. The 'on arrival' readings gave significant values at the 95% level (p<0.05) at Week 4 and at the 99% level (p<0.01) at Weeks 8 and 12.

The 'after heating' readings gave a significant result at the 99% level (p<0.01) only for Week 12. Again there was a correlation between the improvement shown in the mean thermal clearance rates and the outside temperature. After allowing for the influence of the outside temperature the 'significant' results remained significant.

The thermal clearance rates confirmed the relative minor obliterator changes in the skin’s microcirculation but also showed a progressive trend towards improvement even for the 'after heating' values suggesting possible unblocking of partially obstructed vessels.

3. Time required to induce Raynaud's phenomenon
Median, rather than mean, values of the time taken to induce Raynaud's phenomenon were
used for statistical evaluation because in severely affected patients Raynaud’s phenomenon was present on arrival and at Week 12 it was not possible to induce digital blanching in two of the thirty patients within 15 minutes of intense local cooling (Table 7).

The improvement demonstrable with this test of the patients’ microcirculatory function is also demonstrated in Figure 1.

The Wilcoxon matched pairs Signed Ranks test was used to see if there was any significant difference in the times taken to induce Raynaud’s phenomenon at Week 0 compared with Weeks 4, 8 and 12. This increase was highly significant at all three assessments (Weeks 4, 8 and 12: \( p < 0.001 \)).

When the required correction allowing for the warmer outside temperature during the later stages of the study was made, there was still a significant increase at Week 4 (\( p < 0.01 \)) and the increased time required to induce Raynaud’s phenomenon at Week 8 was still highly significant (\( p < 0.001 \)).

The calculations could only be approximate because some patients arrived at the laboratory with white fingers at all stages of this study (Table 8) and in two patients attempts to induce Raynaud’s phenomenon were abandoned after 15 minutes towards the end of the study.

4. Response during reactive hyperaemia tests

All patients showed very poor responses under the test conditions. Only three patients showed reactive hyperaemia at the beginning of the study but eight at its end.

In spite of the low fingertip temperature and thermal clearance responses shown by the trial patients during this very discriminating procedure, a clinical trend, which did not reach significance, appeared towards the end of the trial, implying that a longer trial period might have demonstrated further improvement (Tables 9 and 10).

![Fig. 1 Time taken to induce Raynaud's phenomenon (if not present on arrival) – median values](image-url)
Table 8

Patients with Raynaud's phenomenon present 'on arrival'

<table>
<thead>
<tr>
<th>Primary or secondary Raynaud's phenomenon</th>
<th>Smoker/non-smoker</th>
<th>Time taken to induce Raynaud's phenomenon (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age</td>
<td>Outside temperatures in brackets (°C)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Week: -4 0 4 8 12</td>
</tr>
<tr>
<td>P</td>
<td>27 Non-smoker</td>
<td>0 (3) 0 (3) 0 (7) 0 (7) 50 (14)</td>
</tr>
<tr>
<td>P</td>
<td>36 Non-smoker</td>
<td>120 (3) 0 (2) 180 (9) 300 (8) 0 (7)</td>
</tr>
<tr>
<td>S</td>
<td>53 Non-smoker</td>
<td>0 (4) 140 (6) 220 (10) 335 (15) 560 (14)</td>
</tr>
<tr>
<td>S</td>
<td>68 Non-smoker</td>
<td>0 (3) 180 (5) 300 (7) 480 (11) 720 (18)</td>
</tr>
<tr>
<td>S</td>
<td>40 Non-Smoker</td>
<td>0 (3) 180 (5) 420 (12) 360 (8) 840 (12)</td>
</tr>
<tr>
<td>S</td>
<td>34 Non-Smoker</td>
<td>0 (3) 120 (5) 360 (7) 540 (9) 840 (14)</td>
</tr>
<tr>
<td>S</td>
<td>28 Non-Smoker</td>
<td>0 (3) 50 (5) 90 (8) 230 (7) 410 (11)</td>
</tr>
<tr>
<td>S</td>
<td>48 Smoker</td>
<td>120 (2) 120 (4) 180 (7) 0 (8) 180 (12)</td>
</tr>
<tr>
<td>S</td>
<td>53 Smoker</td>
<td>0 (3) 160 (5) 420 (8) 480 (5) 720 (12)</td>
</tr>
</tbody>
</table>

These measurements support the frequent observation that cold is not the only precipitating factor of attacks of Raynaud's phenomenon in predisposed individuals.

Table 9

Mean skin temperatures attained after cuff release without a 'peak response' being evident (°C)

<table>
<thead>
<tr>
<th>Week number</th>
<th>-4</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>°C mean</td>
<td>29.24</td>
<td>29.57</td>
<td>29.85</td>
<td>30.97</td>
<td>31.58</td>
</tr>
</tbody>
</table>

A t-test to test between the means at Weeks 4, 8 and 12 and that at Week 0 did not show any statistical significance.

Table 10

Mean skin temperatures of the eight patients who showed reactive hyperaemia (with peak responses) during the trial (°C)

<table>
<thead>
<tr>
<th>Week number</th>
<th>-4</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (°C)</td>
<td>30.33</td>
<td>29.93</td>
<td>31.10</td>
<td>31.62</td>
<td>32.44</td>
</tr>
<tr>
<td>Number of patients</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

Table 11

The mean level of cholesterol, triglycerides, fibrinogen, and plasma viscosity at each of the assessments

<table>
<thead>
<tr>
<th>Weeks</th>
<th>-4</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (normal range 3.6–7.8 mmol/l)</td>
<td>Number</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>6.23</td>
<td>6.24</td>
<td>6.00</td>
<td>6.11</td>
</tr>
<tr>
<td></td>
<td>Standard deviation</td>
<td>1.40</td>
<td>1.41</td>
<td>1.30</td>
<td>1.27</td>
</tr>
<tr>
<td>Triglycerides (normal range 0.3–1.7 mmol/l)</td>
<td>Number</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>1.57</td>
<td>1.65</td>
<td>1.46</td>
<td>1.37</td>
</tr>
<tr>
<td></td>
<td>Standard deviation</td>
<td>0.92</td>
<td>1.15</td>
<td>0.88</td>
<td>0.81</td>
</tr>
<tr>
<td>Fibrinogen (normal range 2.0–4.0 g/l)</td>
<td>Number</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>2.53</td>
<td>2.66</td>
<td>2.39</td>
<td>2.27</td>
</tr>
<tr>
<td></td>
<td>Standard deviation</td>
<td>0.51</td>
<td>0.69</td>
<td>0.49</td>
<td>0.53</td>
</tr>
<tr>
<td>Plasma viscosity (upper limit of normal range 1.69 cp)</td>
<td>Number</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>1.758</td>
<td>1.742</td>
<td>1.714</td>
<td>1.715</td>
</tr>
<tr>
<td></td>
<td>Standard deviation</td>
<td>0.125</td>
<td>0.115</td>
<td>0.101</td>
<td>0.113</td>
</tr>
</tbody>
</table>

The means at Weeks 4, 8 and 12 were each tested against the mean at Week 0 using a t-test.
5. Laboratory data
Throughout this study blood counts and liver function tests remained normal in all patients. Table 11 shows the mean level of cholesterol, triglycerides, fibrinogen and plasma viscosity at each of the assessments.

Comments:
1. There was a significant linear fall in cholesterol (p < 0·01), triglycerides (p < 0·025), and of fibrinogen levels (p < 0·01). In the case of fibrinogen there was an increase at 12 weeks relative to 8 weeks and it was found that it was statistically significant (p < 0·01), denoting that there was a deviation from the overall downward trend.
2. Although there was a fall in plasma viscosity levels over the assessment period it was found not to be statistically significant.
3. Age was positively correlated with plasma viscosity levels, but not with cholesterol, triglycerides or fibrinogen levels.
4. High baseline triglyceride levels were associated with low severity scores and high, 'before cooling', fingertip temperatures. High cholesterol levels were also significantly correlated with low severity scores but there was no significant correlation with the 'before cooling' fingertip temperatures.
5. Cholesterol and triglyceride levels were positively correlated at Week 0 but there was no correlation between the change in levels of cholesterol at Week 12, and the change in triglycerides.
6. The plasma viscosity means gave no significant results at any of the assessments but the fibrinogen values gave a significant result at the 95% level (p < 0·05) at Week 8.

6. The effect of cigarette smoking
In order to assess separately the effect of inositol nicotinate upon patients who were cigarette smokers, patients were divided into three groups according to their smoking habits: non-smokers, light smokers (up to 10 cigarettes daily) and heavy smokers (more than 10 cigarettes) and the severity of their digital vasoplastic disease was graded as 'mild-moderate' and as 'moderate'.

Analysis of their test results showed that those who have more severe symptoms and who are heavy smokers required a longer treatment period before they improved, compared with light smokers or non-smokers. None of the smokers had stopped smoking during the trial period.

7. Subjective assessments of symptoms
When at each visit patients were asked about:
(a) pain on exposure to cold,
(b) coldness of extremities,
(c) paraesthesiae,
(d) frequency and severity of attacks of Raynaud's phenomenon and to grade their symptoms as:

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>mild</td>
<td>moderate</td>
<td>severe</td>
</tr>
</tbody>
</table>

the answers shown in Table 12 were obtained.

Using the t-test the means of these gradings of clinical symptoms were compared at Weeks 4, 8 and 12 with mean at Week 0. There was a significant improvement at the 95% level (p < 0·05) at Week 8 for all symptoms except for paraesthesiae. At Week 12 there were significant improvements at the 95% level (p < 0·05) for all symptoms.

When the effect of the improvement in the outside temperature was removed all statistically significant results remained significant.

In spite of these subjective assessments, on direct questioning about the efficacy of inositol nicotinate in the dose of 1 g four times daily seven patients denied any benefit, although their instrumental findings showed a significant improvement of their vasospastic disease, five declared themselves 'slightly improved', eight felt 'moderately improved' and ten were 'very pleased' with its therapeutic effect. Only one patient claimed to get indigestion and occasional nausea from this drug. Six patients disliked the chalky taste of the tablets. None of the patients experienced flushing.
Table 12

Patients’ grading of their symptoms in four arbitrary units (means of all patients)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Week number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-4</td>
</tr>
<tr>
<td>Pain on exposure to cold</td>
<td>1.63</td>
</tr>
<tr>
<td>Coldness of extremities</td>
<td>1.73</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>1.63</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>1.60</td>
</tr>
</tbody>
</table>

Using the t-test the means of these gradings of clinical symptoms were compared at Weeks 4, 8 and 12 with the mean at Week 0. There was a significant improvement at the 95% level (p < 0.05) at Week 8 for all symptoms except for paraesthesia. At Week 12 there were significant improvements at the 95% level (p < 0.05) for all symptoms.

Discussion

For this study of the vaso-active effects of inositol nicotinate in thirty patients with mild to moderately severe vasospastic disease of their digits full use was made of non-invasive experimental techniques in order to assess the digital circulation under strictly controlled and widely varying experimental conditions. The results showed a convincing beneficial therapeutic effect upon patients with primary Raynaud’s phenomenon as well as in those whose Raynaud’s phenomenon was secondary to an obliterative vascular disease.

The earlier impression that this drug requires a fairly prolonged ‘build-up’ period was confirmed by the instrumental and clinical results. Although patients received inositol nicotinate for 12 consecutive weeks some still showed a trend towards further improvement at the end of the trial period. These findings clearly suggest that the therapeutic effect of this drug is not merely due to dilation of the microcirculation but that other mechanisms such as enhanced fibrinolysis may play a significant part in its overall effect.

Many interesting findings, such as the slower response of smokers and responsiveness to this drug even in older age groups with longstanding vasospastic disease were made.

The absence of unwanted side-effects, either clinical or upon the blood constituents or liver function, was gratifying.

Not all patients taking part in this study were convinced of the therapeutic efficacy of inositol nicotinate, but the majority were. In all patients who denied subjective benefit the objective data demonstrated unequivocal improvement of their vascular function. However, it would be unwise to overstate the usefulness of this drug. It does not abolish vascular spasm of the microcirculation in the affected extremities, but it is more effective than most of its competitors. Furthermore, from the author’s personal experience it appears to be non-toxic even when taken in three or four times the dose used during this study. It is certainly useful, together with other measures, in the symptomatic management of vasospastic disease of the extremities. Unlike some other drugs in this field it is effective orally and extremely well tolerated.

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REFERENCES


Holti G (1955) The copper-tellurite-copper thermopile adapted as a skin thermometer. Clinical Science 14, 137


Kappert A (1961) Experimental and clinical investigations with Hexanici. Therapeutische Umschau 18, 303

Sommer H (1965) Nicotinic acid levels in the blood and fibrinolysis under the influence of the hexanicotinic acid ester of m-inositol. Arzneimitte Forschung 15, (11), 1337