SUMMARY. Isradipine is a new potent calcium-channel blocking agent with highly selective action on peripheral vessels. In this single-blind study, its dose-related effect on cold-induced changes in finger systolic pressure (FSP) was investigated in ten female patients with primary Raynaud's phenomenon, and the side effects of isradipine treatment were evaluated. The patients were studied during 9 weeks of treatment. After 3 weeks of placebo, isradipine was given in doses of 1.25 mg b.i.d. and 2.5 mg b.i.d. for 3 weeks each. FSP was measured on local finger cooling to 10°C. FSP at 10°C expressed in percent of the value of 30°C increased from 21 ± 16% (M ± SD) after placebo to 42 ± 28% (p < 0.05) and 62 ± 25% (p < 0.001) after treatment with isradipine 1.25 mg and 2.5 mg b.i.d., respectively. The subjective efficacy of the treatment was assessed with a visual analogue scale (VAS). The VAS rating increased from 17 (range 0-66) after placebo to 39 (range 12-88) (NS) and 68 (range 25-99) (p < 0.001) after isradipine treatment with 1.25 mg and 2.5 mg b.i.d., respectively. Adverse effects of isradipine therapy were few and did not differ from those reported after the placebo period. This single-blind, dose-response study showed that isradipine in doses of 1.25 mg and 2.5 mg b.i.d. had favorable objective and subjective effects in patients with primary Raynaud's phenomenon and had no serious side effects.

KEY WORDS. Raynaud's phenomenon, isradipine, vasodilatation, calcium channel antagonist, adverse effects

Digital vasospastic disease or Raynaud's phenomenon was first described by M. Raynaud in 1862. It is a common disorder. Female patients outnumber male patients by five to one [1]. In a study of a random female population sample aged 18-59 years in Sweden, 15.6% were diagnosed as having Raynaud's phenomenon [2].

Different types of drug therapy have been used, with varying degrees of success, in patients suffering from disabling Raynaud's phenomenon. Some calcium antagonists—particularly nifedipine and diltiazem—have been found to be effective in several studies [3-7], but troublesome side effects may occur. It is therefore important to evaluate the effects of other calcium antagonists on cold-induced vasospasm in relation to their possible adverse effects.

Isradipine (PN 200-110), a dihydropyridine derivative [(4-benzofurazanol)-1,4-dihydro-2,6-dimethyl-3, 5-pyridinedicarboxyllicacid, 2-methyl 5-(1 methylethyl)-ester], has been found to act as a potent calcium-channel blocking agent in laboratory animals [8]. This drug is a very strong antagonist of depolarization-induced contraction in blood vessels of various origins. In human smooth muscle studied postmortem, isradipine was very potent in inhibiting contractions elicited by an increase in the potassium concentration [9].

The aims of the present study were:

- to evaluate the effect of isradipine in doses of 1.25 mg b.i.d. and 2.5 mg b.i.d. on cold-induced vasospasm in patients with disabling primary Raynaud's phenomenon and
- to evaluate tolerance to the treatment and reported adverse reactions.

Patients

The study comprised ten female patients, with a mean age (± SD) of 43 ± 7 years, who had disabling primary Raynaud's phenomenon for a mean period (± SD) of 12...
± 6 years and who had a finger systolic pressure (FSP) at 10°C below 50% of the value at 30°C. The Raynaud’s phenomenon had not been treated previously. The patients were selected from a population studied earlier with respect to this phenomenon [2]. All the patients gave informed consent and were willing to attend all clinic visits and examinations. The study complied with the code of ethics of the Declaration of Helsinki and was approved by the local ethics committee.

Methods

Measurement of Finger Systolic Pressure

The subjects were investigated in the supine position with the most affected hand resting on a platform at midaxillary level. After 20 minutes of rest, FSP was measured in the test finger (FSPt) and in a control finger (FSPc), using an occlusion cuff on the middle phalanx and a strain gauge on the distal phalanx. The test finger was the finger with the most pronounced symptoms and the control finger was another finger on the same hand. A water-chilled blanket at a temperature of 13.5 ± 1.5°C (SD) was then applied, covering the body from chin to feet, to standardize the environmental temperature [10]. After 30 minutes of body cooling under the blanket, the double-inlet occlusion cuff on the test finger was perfused with water for 5 minutes to warm or cool the test finger to 30°C or 10°C, respectively. At each temperature level, the systolic blood pressure was measured in the test finger, the control finger, and in the brachial artery. The blood pressure measurements were performed twice at each temperature level. The change in FSP on cooling to 10°C was expressed in percent of the FSP at 30°C with correction for changes in systemic blood pressure (see formula).

\[
\text{FSP\%} = \frac{\text{FSP/t10} \times 100}{\text{FSP/t30} - (\text{FSP/c30} - \text{FSP/c10})}
\]

where

- FSP/t10 = finger systolic pressure in test finger at 10°C,
- FSP/t30 = finger systolic pressure in test finger at 30°C,
- FSP/c10 = finger systolic pressure in control finger at 10°C,
- FSP/c30 = finger systolic pressure in control finger at 30°C.

The traces were read blindly by one observer (I.R.), who neither made the recording nor knew to which group the subjects belonged.

The reproducibility of the method was evaluated in a previous study in 28 patients with primary and secondary Raynaud’s phenomenon (vibration-induced white finger). The correlation between two separate measurements at 10°C was 0.88 (p < 0.001) [7].

Subjective Assessment of the Efficacy of the Treatment of Primary Raynaud’s Phenomenon

The patients assessed the efficacy of the treatment on a visual analogue scale (VAS). The scale started at 0, i.e., no problems with cold and white fingers, and ended with 100, i.e., considerable problems.

Study Design

The study was single blind (the patients did not know what kind of treatment they received during the study), and the total duration of treatment was 9 weeks. After an initial placebo run-in period of 3 weeks, the patients were given isradipine capsules in a dose of 1.25 mg b.i.d. for 3 weeks followed by 2.5 mg for a further 3 weeks. No vasoactive compounds other than isradipine were taken. At the end of each period, FSP was measured and the patients were questioned regarding side effects; they also assessed the efficacy of the therapy on a visual analogue scale.

Statistical Analysis

Student’s t-test for paired observations was used to evaluate the changes in the investigated variables. The side effects were assessed with the McNemar test. The values reported below are mean ± standard deviation.

Results

The mean systemic systolic BP was significantly lower only after treatment with isradipine 2.5 mg b.i.d., compare with the placebo period (108 ± 10 mmHg vs. 122 ± 17 mmHg (p < 0.05)).

The heart rate was unchanged after treatment with isradipine, both at the lower and at the higher dose, compared with placebo (68 ± 9, 61 ± 6, 63 ± 5, respectively).

The mean FSP% measured at 10°C was 21 ± 16% after the placebo period. It increased to 42 ± 28% after