Scand J Rehab Med 16: 159–162, 1984

THE EFFECTS OF PHYSICAL TRAINING AND FLUNARIZINE ON WALKING CAPACITY IN INTERMITTENT CLAUDICATION

Mauri Lepäntalo, Stig Sundberg and Ariel Gordin

From the Fourth Department of Surgery, Helsinki University Central Hospital, Helsinki and Clinical Research Department, Orion Pharmaceutical Co., Espoo, Finland

ABSTRACT. The clinical significance of drugs improving red cell deformability is not confirmed. We established the effect of physical training alone and combined with flunarizine on intermittent claudication. Twelve patients aged 48–73 years were included in the study. Pain-free walking distance on treadmill, ankle/arm pressure ratio and transcutaneous oxygen tension were measured. Walking distance increased significantly ($p<0.05$) by 130 % from 75 m to 173 m during the first year when the patients were on programmed physical training. Ankle/arm pressure ratio also increased significantly ($p<0.05$) from 0.46 to 0.55 during this period. The increase in walking distance ceased when the programmed physical training was discontinued for 6 months. During the following double-blind, cross-over medication period the patients were given flunarizine 5 mg b.i.d. and placebos in randomized order for 3 months each. They also continued the same programmed physical training as during the first year. Walking distance increased, albeit not significantly, with time to 392 m after the second medication period. There was no difference, however, between flunarizine and placebo. Ankle/arm pressure ratio was of the same magnitude as at the beginning of the trial. Oxygen tension measurements did not give consistent results. We conclude that programmed physical training increased walking distance as a function of time. Flunarizine had no effect on the performance of patients with intermittent claudication.

Key words: Intermittent claudication, walking distance, ankle/arm blood pressure ratio, physical training, flunarizine

Increasing physical training and giving up smoking are the first measures taken in the treatment of arterial insufficiency of the lower extremities (1, 2, 5). Drug therapy has also been tried widely, but there is no clear evidence of its usefulness (12). A recent trend is to use drugs improving red cell deformability, thus increasing circulation of ischemic areas. Flunarizine, which inhibits entrance of calcium into the smooth muscle of the arterial wall has been shown to also improve impaired red cell deformability in patients with arteriosclerosis (3). The clinical significance of this mechanism has not been confirmed so far.

The purpose of the study was to follow any changes in walking capacity during 1.5 years of physical training and in a cross-over, double-blind manner to compare flunarizine and placebo for efficacy in patients with intermittent claudication.

METHODS

The study included 12 patients with intermittent claudication due to peripheral arterial disease as confirmed by ankle/arm pressure ratio measurements (10). Patients with performance-limiting cardiac symptoms and severe hypertension (WHO III) were excluded.

None of the patients had undergone arterial surgery of the lower extremities. The mean age of the patients was 60 years (range 48–73 years). There were 8 men and 4 women with intermittent claudication for 1–6 years (mean 3.5 years). Two of the patients had insulin-dependent diabetes; none were on β-blockers. Five were smokers, 4 had given up smoking and 3 were nonsmokers. Informed consent was obtained from all patients and the study was approved by the Ethical Committee of IV Department of Surgery, Helsinki University Central Hospital.

The study was divided into five periods. During the first two periods (6 months each), the patients followed programmed physical training which was monthly controlled by a physiotherapist. The patients recorded the time they used for the training. During the third period (1–12 months, $\bar{x}$=6 months), the patients trained only according to their own activity, with no controls nor records.

The programmed physical training consisted of different kinds of dynamic exercises of the leg muscles performed every day as taught by a physiotherapist. In addition to their daily activities, the patients were encouraged to take daily walks at least to onset of claudication pain.

The actual drug investigation started upon termination of the third period. The patients were given randomly flunarizine 5 mg twice daily and identical appearing placebo twice daily. The first medication period lasted 3

Table I. *Clinical parameters in 12 patients with intermittent claudication*
Mean and SEM are given

	Baseline	Programmed training		Programmed training discontinued
		1st period	2nd period	3rd period
Pain-free walking distance (m)	75±10	156±30	173±44	165±51
Ankle/arm pressure ratio	0.46±0.03	0.50±0.03	0.55±0.04	0.50±0.05
$TcpO_2$ (mmHg)[c]	–	–	–	45±5
Recovery time (min)[c]	–	–	–	4.3±0.8

[a] In chronological order.
[b] Treatments specified irrespective of order of administration.
[c] $n=11$.

months (fourth period), during which the patients trained again under the supervision of the physiotherapist as above. Hereafter medication was changed, and this period, too, lasted 3 months (fifth period). The fifth period was otherwise identical with the fourth period.

At the end of each period, pain-free and maximal walking distance on a treadmill and ankle/arm pressure ratio were recorded. At onset of the actual drug investigation and at the end of each medication period, further measurements included transcutaneous oxygen tension at standard spots in the foot and determinations of B-Hb, B-Hct, B-MCHC, B-leuk, S-GOT, S-alkaline phosphatase, S-GPT, S-creat, U-prot and U-gluc.

The walking test was performed on a treadmill, with a speed of 3.6 km/h and elevation 0°. The distance when the patient reported onset of claudication pain (pain-free walking distance) was measured. Maximal walking distance could not be applied, because seven of the patients never experienced symptoms severe enough to make them stop the walking test which was maximally 10 min for the training and 20 min for the medication plus training period. All patients had walked on a treadmill several times before the trial.

Blood pressure was measured supine from both arms with a mercury sphygmomanometer and systolic blood pressure from both ankles with a Doppler device. The ratio between the systolic blood pressure in the ankle and arm was calculated with the higher arm pressure recording as reference value. The calculation was performed for both legs.

The oxygen tension was measured with a transcutaneous oxygen electrode (Radiometer) (6, 8) in the more affected foot. Arterial circulation of the foot was thereafter occluded for five minutes with a blood pressure cuff by applying a pressure 50 mm Hg higher than the systolic pressure. During postocclusive reactive hyperemia, the time for the oxygen tension to return to baseline value (recovery time) was measured (7). Side effects were questioned about during the drug investigation using specific questionnaires. Two-way analysis of variance and Scheffe's multiple comparison method were used to test differences between periods. A p-value <0.05 was considered statistically significant.

RESULTS

Testing of pain-free walking distance for all periods with the analysis of variance gave $p<0.05$. Scheffe's multiple comparison did not, however, reveal significant differences between the periods. There was no difference between flunarizine (315 m) and placebo (299 m). For further analyses, the medication periods were placed in a chronological order. Even now a statistical significance ($p<0.001$) was reached with the analysis of variance and Scheffe's multiple comparison showed the second medication period (irrespective of whether flunarizine or placebo had been administered to differ significantly ($p<0.01$) from the baseline value (392 m vs. 75 m).

During the first year, when the patients followed programmed physical training, the pain-free walking distance increased by 130% as compared to the baseline value. The analysis of variance gave $p<0.05$ and Sceffe's multiple comparison showed that there was a statistically significant ($p<0.05$) difference between the second period (173 m) and the baseline value (75 m) the greatest difference occurring, however, during the first 6 months.

With regard to ankle/arm pressure ratio, the analysis of variance gave $p<0.05$ for all periods when the periods were in chronological order, but according to multiple comparison, there was no statistically significant differences. For the two first periods with the patients on programmed physical training, the analysis of variance gave $p<0.05$. Scheffe's multiple comparison showed the value of the second period (0.55) to be significantly ($p<0.05$) higher than the baseline value (0.46). Ankle/arm pressure ratio was, however, of the same magni-

Medication + programmed training

1st drug	2nd drug[a]	Flunarizine	Placebo[b]
221±63	392±131	315±120	299±89
0.52±0.05	0.44±0.06	0.49±0.06	0.48±0.06
39±5	41±5	38±5	42±6
4.1±0.9	3.6±0.4	3.3±0.6	4.5±0.8

tude after the fifth period (0.44) as at the beginning of the trial.

As to oxygen tension and recovery time, there were no significant differences (Table I). This could in part, at least, be explained by the considerable scattering.

No changes, as a rule, occurred in the laboratory parameters. However, S-alkaline phosphatase was slightly elevated in one patient and S-GPT in another during the entire study.

Only side effects which the patient experienced on either medication period and which were at least moderate in severity (scale: mild, moderate, severe) were considered (Table II). Despite the fact that statistically significant differences (binomial test) between flunarizine and placebo could not be obtained due to the small material size, it seems evident that flunarizine more often caused drowsiness and fatigue.

DISCUSSION

The positive effect of physical training on walking has been observed in several earlier studies (2, 4, 9). The present study did, however, reveal quite well the fact that the favourable trend achieved by physical training was interrupted by discontinuation of programmed physical training. This finding implies to the unability of the patients to be consistent enough to carry on the training program without supervision and encouragement by a physiotherapist.

Table II. *Number of side effects reported by 12 patients with intermittent claudication*

	Flunarizine	Placebo
Drowsiness	4	–
Fatigue	5	–
Itching	–	2

The increase in the ankle/arm pressure during the first year of the present trial was an unexpected finding, even though Skinner & Strandness (11) did observe in their material of five patients the resting ankle blood pressure to increase as a result of 3–8 months of physical training. They interpreted this to be due to the exercise-related improved collateral blood flow. In most studies, maximal calf blood flow did not improve, however, despite the significant improvement in walking performance (2, 4, 9, 13). Our two-year results are in accordance with these observations. The positive effect of physical training on walking performance is evidently due rather to local circulatory (2, 13) or metabolic changes (4) in the leg musculature than to an increase in the net limb flow.

Measurement of transcutaneous oxygen tension turned out to be a rather inaccurate method for repeated measurements of drug effects on peripheral circulation at least in our hands.

It may be concluded that programmed physical training increased pain-free walking distance as a function of time. Flunarizine had no effect on the walking capacity of patients with intermittent claudication. This could be due to lack of effect on blood/plasma viscosity and red cell deformability. We did not include measurements of rheological variables in the present study. However, in a recent investigation (14) flunarizine was found to improve red cell deformability without changes in blood/plasma viscosity in patients with intermittent claudication.

REFRENCES

1. Clifford, P. C., Davies, P. W., Hayne, J. A. & Baird, R. N.: Intermittent claudication: Is a supervised exercise class worth while? Br Med J *280:*1503, 1980.
2. Dahllöf, A. G., Holm, J., Scherstén, T. & Sivertsson, R.: Peripheral arterial insufficiency; effect of physical training on walking tolerance, calf blood flow and blood flow resistance. Scand J Rehabil Med *8:*19, 1976.
3. De Cree, J., De Cook, W., Geukens, H., De Clerck, F., Beerens, M. & Verhaegen, H.: The rheological effects of Cinnarizine and Flunarizine in normal and pathologic conditions. Angiology *30:*505, 1979.
4. Ekroth, R., Dahllöf, A. G., Gundevall, B., Holm, J.

& Scherstén, T.: Physical training of patients with intermittent claudication: indications, methods, and results. Surgery *84:*640, 1978.
5. Ericsson, B., Haeger, K. & Lindell S.-E.: Effect of physical training on intermittent claudication. Angiology *21:* 188, 1970.
6. Friis-Hansen, B., Marstrand-Christiansen, P. & Vesterager, P.: Transcutaneous measurement of arterial blood oxygen tension with a new electrode. Scand J Clin Lab Invest *37:* Suppl. 146: 31, 1977.
7. Fronek, A., Franzeck, U. & Bernstein, E. F.: Transcutaneously monitored pO_2 post occlusive reactive hyperemia response (abstr). VI Annual San Diego Symposium. Noninvasive diagnostic techniques in vascular disease. San Diego, 1979, Sept. 10–14.
8. Göthgen, I. & Jacobsen, E.: Transcutaneous oxygen tension measurement. I. Age variation and reproducibility. Acta Anesthesiol Scand, Suppl. *67:*66, 1978.
9. Larsen, O. A. & Lassen, N. A.: Effect of daily muscular exercise in patients with intermittent claudication. Lancet *2:*1093, 1966.
10. Lepäntalo, M., Lindfors, O. & Pekkola, P.: The ankle/arm blood pressure ratio as a screening test for arterial insufficiency in the lower limb. Ann Chir Gyn *72:*57, 1983.
11. Skinner, J. S. & Strandness, D. E.: Exercise and intermittent claudication. II. Effect of physical training. Circulation *36:*23, 1967.
12. Verstraete, M.: Current therapy for intermittent claudication. Drugs *24:*240, 1982.
13. Zetterquist, S.: The effect of active training on the nutritive blood flow in exercising ischemic legs. Scand J Clin Lab Invest *25:*101, 1970.
14. Perhoniemi, V., Salmenkivi, K., Sundberg, S., Johnsson, R. & Gordin, A.: Effects of flunarizine and pentoxifylline on walking distance and blood rheology in claudication. Angiology, 1984 (in press).

Address for offprints:

Mauri Lepäntalo, M. D.
Helsinki University Central Hospital
4th Department of Surgery
Kasarmikatu 11
SF-00130 Helsinki 13
Finland