A randomized, double-blind, placebo-controlled, crossover study to assess the immediate effect of sublingual glyceryl trinitrate on the ankle brachial pressure index, claudication, and maximum walking distance of patients with intermittent claudication

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Purpose: **The goal of the present study was to assess the immediate effect of sublingual glyceryl trinitrate (GTN) in patients with intermittent claudication.**
Methods: **We conducted a randomized, double-blind, placebo-controlled crossover study. Inclusion criteria consisted of history of intermittent claudication, resting ankle brachial pressure index (ABPI) of 1.00 or less, a 20% or greater fall in ABPI after exercise, and maximum walking distance (MWD) of less than 250 m. Patients already receiving nitrates were excluded. In study 1, patients (n = 25) underwent a standard exercise test after randomization to receive either 800 µg of sublingual GTN or placebo. The post-exercise ABPI was recorded. Then, the crossover portion of the study was performed. In study 2, patients (n = 22) had their claudication distance and MWD measured. They then were randomized to receive either GTN or placebo spray, and the exercise test was repeated, with the claudication distance and MWD recorded, followed by the crossover portion of the study. Statistical analysis was performed with the Wilcoxon matched pairs signed ranks test and the Mann-Whitney *U* test.**
Results: **In study 1, the median postexercise ABPIs for placebo and GTN were 0.29 and 0.36 (*P* = .0001). In study 2, the median claudication distance for both placebo and GTN groups was 70 m (*P* = .59). The median MWD for the placebo and GTN groups was 105 and 125 m (*P* = .0084)**
Conclusion: **GTN can decrease the fall in ABPI after exercise and increase the MWD. (J Vasc Surg 1998;28:895-900.)**

Intermittent claudication is a common and debilitating condition. Approximately 0.5% to 2% of men aged 45 to 69 years will have symptoms of intermittent claudication.[1,2] The majority are treated conservatively. In 1959, Gillespie wrote that "as vasodilators do not increase calf muscle blood flow, and often decrease it, prescribing them for intermittent claudication is useless."[3] Since that time, a number of drugs have been tried in patients with intermittent claudication with limited success.

The discovery that nitric oxide is a potent vasodilator of both arteries and veins lead us to reassess the role of nitrates in intermittent claudication. Previous studies investigating the use of nitrates in claudication looked at the long-term administration of nitrates and the subsequent effect.[4] A problem with such studies is that it may be difficult to distinguish a direct pharmacological effect from the effect of development of a collateral circulation. Even with no treatment, 75% of patients with intermittent claudication will have an improvement in or stabilization of their symptoms.[5] Our aim

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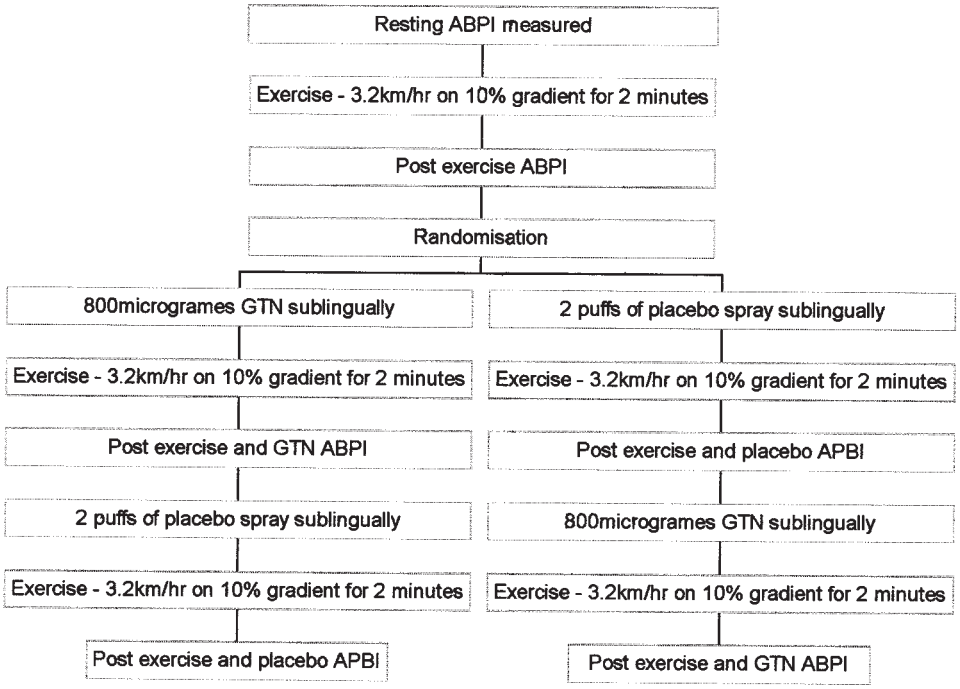

Fig 1. Flow diagram to summarize study 1.

Table I. Patient demographics for studies 1 and 2

	Study 1	*Study 2*
Number of patients	25	22
Median age (interquartile range)	70 (59 to 75)	69 (60 to 73)
Male	18	16
Smoker	7	5
Diabetic	5	3

was to assess the immediate effect of a single dose of sublingual GTN in patients with intermittent claudication; this would measure an immediate pharmacological effect rather than an effect due to the development of a collateral circulation.

PATIENTS AND METHODS

Study 1. This study was performed to determine whether GTN made an objective difference to the ankle brachial pressure index (ABPI) after a standardized exercise test compared with placebo. Patients (n = 25) of a median age of 70 years (age range, 59 to 75 years; 18 men and 7 women; 7 smokers; 5 diabetics) who were attending the vascular laboratory for treadmill assessment of their intermittent claudication were recruited (Table I). Inclusion criteria were (1) a history of intermittent claudication, (2) a resting ABPI of 1.00 or less, and (3) a 20% or greater fall in ABPI after a standard exercise test. Patients already receiving nitrates were excluded. The resting ABPI was assessed with a sphygmomanometer, and a hand-held Doppler was used to record the brachial artery pressure and the maximum ankle pressure in either the dorsalis pedis, posterior tibial, or peroneal artery. The protocol is summarized in Fig 1. The standard exercise test was performed using a treadmill set at 3.2 km/h on a 10% gradient for 2 minutes. If the patients could not manage this protocol, the maximum speed and time they could manage was recorded, and this same regimen was used for all subsequent tests for each individual. Postexercise ABPI was recorded, and the patient was immediately returned to the treadmill. Patients then were randomized by computer-generated random numbers to receive either 800 μg of sublingual GTN by a metered-dose spray ($t_{1/2}$ = 2.5 minutes) or two puffs of a placebo spray. The exercise was repeated at the same speed and for the same length of time as in exercise 1. The postexercise ABPI was recorded, and this was followed immediately by the cross-over portion of the study, with patients receiving either GTN or placebo spray before repeating exercise 1, followed by repeat measurement of the ABPI. At completion, patients were asked whether they had developed a headache. Double blinding was achieved by the drug or place-

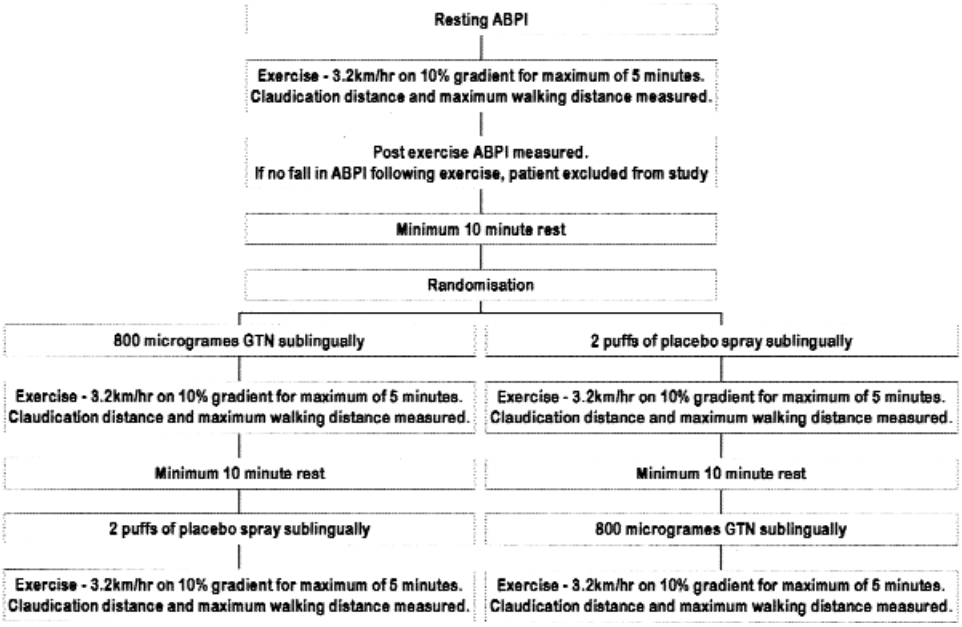

Fig 2. Flow diagram to summarize study 2.

bo being administered by an independent observer such that patient and technician were unaware of the formulation used.

Study 2. This study was performed to determine whether GTN had any effect on the claudication distance (CD) and maximum walking distance (MWD) compared with placebo. Patients (n = 22) of a median age of 69 years (age range, 60 to 73 years; 16 men and 6 women; 5 smokers; 3 diabetics) who were attending the vascular laboratory for treadmill assessment of their intermittent claudication were recruited (Table I). Inclusion criteria were the same as those in study 1. Patients already receiving nitrates were excluded. The protocol is summarized in Fig 2. The ABPI was measured, and then the patients walked on a treadmill set at 3.2 km/h on a 10% gradient. The distance to the onset of claudication pain was recorded (CD). They then were asked to walk for as long as they could tolerate the pain so the MWD could be recorded. Patients were blinded to the reading on the tachometer on the treadmill. The postexercise ABPI then was recorded. Eligible patients were given a rest of 10 minutes from the time of completing the exercise to remounting the treadmill. At this time, they were randomized to receive either 800 μg of GTN or a placebo spray, as in study 1. The exercise was repeated, and patients were asked to indicate the onset of claudication pain. They then were asked to walk for as long as they could tolerate the pain. After an additional 10-minute rest, the cross-over portion of the study was completed, with either GTN or placebo spray being administered before the final exercise test. At completion, patients were asked whether they had developed a headache.

Both studies were of randomized, double-blind, placebo-controlled design. Written informed consent was obtained from patients, and the study was approved by the local ethics committee. A Medicines (exemption from licenses, special cases, and miscellaneous provisions) order 1972 had been obtained.

The diagrams produced for the results visually suggest that the data were not normally distributed. Using a statistical software package, three different tests on our data confirmed them to be not normally distributed (Kurtosis, Skewness, and Kolmogarov-Smirnov goodness-of-fit test for normal distribution); therefore, nonparametric tests were used. Results in the text are expressed as median values (interquartile range) unless stated otherwise, and statistical analysis was performed with Wilcoxon's matched pairs signed rank test for related pairs and the Mann-Whitney *U* test for unrelated pairs.

RESULTS

Study 1. To exclude possible temporal and carryover effects, results were first analyzed according to whether GTN or placebo was administered first.

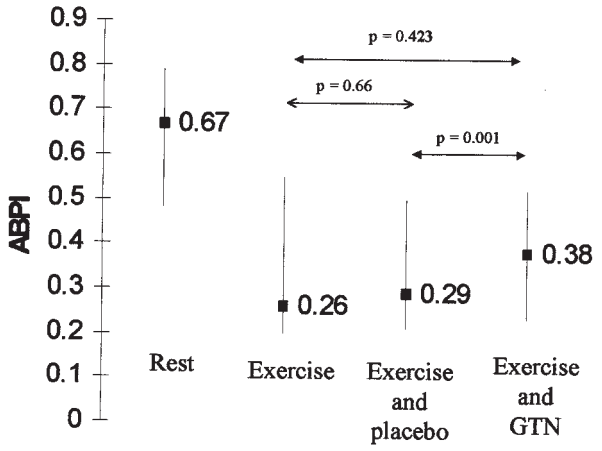

Fig 3. The change in ABPI as shown in study 1. Vertical lines represent interquartile range with median values.

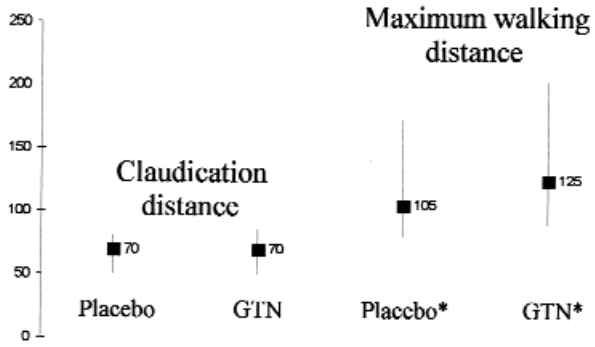

Fig 4. The MWD and CD in meters as shown in study 2. Vertical lines represent interquartile range with median values.

These results are summarized in Table II; they confirm that there was no such effect. Fig 3 shows the pooled results. The median resting brachial pressure was 170 mm Hg (range, 150 to 190 mm Hg), and the median maximum ankle pressure was 100 mm Hg (range, 80 to 125 mm Hg), giving a median resting ABPI of 0.67 (range, 0.47 to 0.79). After exercise and placebo spray, the median brachial pressure was 190 (159 to 210), and the median maximum ankle pressure was 50 mm Hg (40 to 80 mm Hg), giving a median ABPI of 0.29 (0.2 to 0.50). After exercise and GTN, the median brachial pressure was 180 mm Hg (150 to 198 mm Hg), and the median maximum ankle pressure was 60 mm Hg (40 to 90 mm Hg), giving a median ABPI of 0.38 (0.22 to 0.52). The exercise-induced fall in ABPI was lower in patients after GTN compared with placebo (P = .0001). When the placebo maximum ankle pressure was compared with the GTN maximum ankle pressure, there was no significant difference (P = .3), and when the brachial pressures were compared, there was no significant drop in the pressure after GTN compared with placebo (P = .157). Only 1 patient had a headache, and because the study design required placebo and GTN to be administered in rapid succession, it was not possible to determine whether this occurred with GTN or placebo.

Study 2. To exclude possible temporal and carryover effects, results were first analyzed according to whether GTN or placebo was given first. These results are summarized in Table III and indicate that no such effects had occurred. For the entire group, the median ABPI at rest was 0.57 (range, 0.46 to 0.64). The median CDS after placebo and GTN spray were identical at 70 m (range, 50 to 80 m for placebo and 50 to 85 m for GTN; P = .5). The MWD after placebo was 105 m (80 to 172.5 m), and the MWD after GTN was 125 m (90 to 202.5 m; Fig 4). There was a significant improvement (19%) with GTN (P = .0084). Three patients in this study had headache, all occurring after GTN.

DISCUSSION

Assessments of the long-term clinical effects of a drug on claudication are notoriously difficult. One of the main reasons for this is that many patients improve spontaneously, usually within 12 months of the onset of symptoms.[8] The selection of patients who would benefit from intervention is difficult, and because drug therapy has in the past proved to be disappointing, most patients are managed conservatively. The aim of study 1 was to assess the objective effect of GTN on the ABPI after exercise in patients with intermittent claudication. The design of both studies took into account the short half-life of the GTN spray, which is 2.5 minutes (as provided by Lipha Pharmaceuticals Limited). We have shown how the ABPI after exercise decreases less with GTN compared with placebo. The biggest contribution to this is the brachial pressure. In all patients after exercise, the brachial pressure increased; however, this increase was less with GTN than with placebo (P = .016). Thus, although the brachial pressure does not rise as much with GTN, the index improves as the ankle pressure remains much the same. Measurement of the ABPI after exercise is a reliable noninvasive method of quantifying exercise ischemia in patients with intermittent claudication.[6,7] The importance of the ABPI is that because it is a ratio, it allows a com-

Table II. A summary of the results of study 1 according to whether GTN or placebo was administered first

		GTN first			*Placebo first*	
Number of patients	14			11		
Median baseline postexercise ABPI (range)	1	0.46	(0.17 to 0.77)	2	0.20	(0.16 to 0.84)
Median postexercise and placebo ABPI (range)	3	0.31	(0.17 to 0.67)	4	0.25	(0.14 to 0.94)
Median postexercise and GTN ABPI (range)	5	0.53	(0.18 to 0.70)	6	0.30	(0.16 to 1.0)

Comparisons	*Statistical test*	*P*
1 vs 3	Wilcoxon	.4
2 vs 4	Wilcoxon	1.0
3 vs 4	Mann-Whitney *U*	.35
5 vs 6	Mann-Whitney *U*	.12

Table III. A summary of the results of study 2 according to whether GTN or placebo was administered first

		GTN first			*Placebo first*	
Number of patients	13			9		
Median baseline CD (range)	1	50	(30 to 110)	2	50	(20 to 160)
Median baseline MWD (range)	3	130	(80 to 240)	4	100	(50 to 210)
Median CD after placebo (range)	5	70	(40 to 100)	6	70	(30 to 80)
Median MWD after placebo (range)	7	120	(60 to 200)	8	90	(50 to 210)
Median CD after GTN (range)	9	60	(20 to 140)	10	70	(20 to 110)
Median MWD after GTN (range)	11	130	(70 to 240)	12	90	(40 to 250)

Comparisons	*Statistical test*	*P*
1 vs 5	Wilcoxon	.04 (placebo > baseline)
2 vs 6	Wilcoxon	.31
3 vs 7	Wilcoxon	.06
4 vs 8	Wilcoxon	.57
5 vs 6	Mann-Whitney *U*	.76
9 vs 10	Mann-Whitney *U*	.63
7 vs 8	Mann-Whitney *U*	.24
11 vs 12	Mann-Whitney *U*	.18

parison of the degree of ischemia in patients with differing systemic arterial pressures. The implication of this is that GTN produces an improvement in the ABPI after exercise, but this may be due to its systemic effect on arterial pressure rather than to local actions on the arteries within the leg.

For patients, the distance they can walk before the onset of pain (CD) and distance they can walk before the pain forces them to stop walking (MWD) are the important determinants of the degree of disability caused by the arterial disease. It is unclear why in study 2 GTN should improve the MWD but not the CD. However, the MWD is the most important to the patient, and this increased by 19% after a single dose, which can be repeated as necessary. We are currently investigating the effect of repeated doses on the MWD, and this should provide data on the true clinical benefit.

GTN is inexpensive and well tolerated and has been proved to be simple to use. Further investigation is required regarding the mechanism of action and clinical effectiveness in the long term if GTN is to be used in the treatment of intermittent claudication.

In conclusion, we have shown that a single dose of GTN before exercise can improve the ABPI and MWD. The mechanism for this and the clinical application remain to be determined.

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