Angiology
http://ang.sagepub.com/

Study of the Antiischemic Action of EGb 761 in the Treatment of Peripheral Arterial Occlusive Disease by TcPo2 Determination

X. Mouren, Ph. Caillard and F. Schwartz

ANGIOLOGY 1994 45: 413
DOI: 10.1177/000331979404500601

The online version of this article can be found at:
http://ang.sagepub.com/content/45/6/413

Published by:
SAGE
http://www.sagepublications.com

Additional services and information for *Angiology* can be found at:

Email Alerts: http://ang.sagepub.com/cgi/alerts

Subscriptions: http://ang.sagepub.com/subscriptions

Reprints: http://www.sagepub.com/journalsReprints.nav

Permissions: http://www.sagepub.com/journalsPermissions.nav

Citations: http://ang.sagepub.com/content/45/6/413.refs.html

>> Version of Record - Jun 1, 1994

What is This?

Downloaded from ang.sagepub.com at University of British Columbia Library on November 23, 2014

Angiology
The Journal of Vascular Diseases

VOLUME 45 JUNE 1994 NUMBER 6

Study of the Antiischemic Action of EGb 761 in the Treatment of Peripheral Arterial Occlusive Disease by $TcPo_2$ Determination

X. Mouren, M.D., F.A.C.A.
Ph. Caillard, M.D.
and F. Schwartz, M.D.*

PARIS, FRANCE

ABSTRACT

In a randomized, placebo-controlled, double-blind, parallel study of 20 patients, the antiischemic effect of EGb 761 (Ginkgo biloba Extract) was studied by measuring the transcutaneous partial pressure of oxygen ($TcPo_2$) during exercise. Transcutaneous oximetry during exercise provides a good, noninvasive estimation of local arterial perfusion and constitutes a real index of local and regional capillary perfusion.

Twenty patients between the ages of forty-four and seventy-three years suffering from claudicating atherosclerotic arterial occlusive disease in stage II according to the Leriche and Fontaine classification, diagnosed for more than a year and stable for three months, were included.

The eligible patients received placebo for fifteen days under single-blind conditions. At the end of this preinclusion period, the eligibility criteria were checked and the patients were randomized to two treatment groups. The first group received 320 mg per day of EGb 761 for four weeks and the second group received placebo. The treadmill walking test was performed under standardized conditions at the same time of day and by the same investigator.

In a comparison of the differences before and after treatment, the areas of ischemia decreased by 38% in the EGb 761 group but remained essentially stable (+5%) in the placebo group. This difference between groups is significant ($F\ [1.18]=4.91$; $P=0.04$) and the 95% confidence interval for the difference ranges from 0.89 to 3.87.

This study confirmed significantly the rapid antiischemic action of EGb 761 and its value in the management of peripheral arterial occlusive disease at the stage of intermittent claudication.

From the Department of Vascular Exploration, Hôpital Tenon, and *IPSEN, Paris, France

©1994 Westminster Publications, Inc., 708 Glen Cove Avenue, Glen Head, NY 11545, U.S.A.

Downloaded from ang.sagepub.com at University of British Columbia Library on November 23, 2014

Introduction

Transcutaneous oximetry or measurement of the transcutaneous partial pressure of oxygen ($TcPo_2$) during exercise provides a good, noninvasive estimation of local arterial perfusion and constitutes a real index of local and regional capillary perfusion.[1]

The efficacy of standardized and titrated Ginkgo biloba Extract (EGb 761) in stage II peripheral arterial occlusive disease, according to the Leriche and Fontaine classification, has been demonstrated on the basis of validated clinical criteria (claudication distance, ankle systolic pressure during exercise).[2] The present study was designed to evaluate the tissue antiischemic effect of EGb 761 by measuring the $TcPo_2$.

Materials and Methods

Design

Twenty patients between the ages of forty-four and seventy-three years, followed up on an outpatient basis, participated in this study. All patients suffered from claudicating atherosclerotic arterial occlusive disease of the lower extremities diagnosed for more than a year and stable for three months. The severity and topography of the arterial lesions had been documented by arteriography and/or Doppler studies.

This was a double-blind, placebo-controlled study conducted in parallel groups. Randomization was preceded by a fifteen-day preinclusion period, during which the patient received a placebo. This preinclusion phase allowed verification of the inclusion criteria, washout of prohibited concomitant treatments, and familiarization of the patient with health and dietary advice and with the treadmill test. At the end of this preinclusion period, the patients were randomized to two treatment groups. The first group received 320 mg per day of EGb 761 in two divided doses, morning and evening, for four weeks and the second group received placebo.

Patients had to be between the ages of thirty-five and seventy-five years and had to give their consent freely. They were carefully examined to confirm the following eligibility criteria: a claudication distance on the treadmill test under standardized conditions (speed: 3.2 kph, slope: 10%, constant temperature) greater than 100 meters and less than 500 meters and a normal resting $TcPo_2$, ie, greater than 40 mm Hg, measured at the first intermetatarsal space. Patients with stage III and IV arterial disease, recent acute arterial occlusions, or any form of peripheral circulatory insufficency due to causes other than atherosclerosis were not included. Patients in whom surgical revascularization was scheduled during the six months following the study or those with decompensated heart failure, coronary insufficiency, or severe or poorly controlled hypertension were also not included. A locomotor handicap of cerebral, respiratory, or rheumatic origin, likely to make the treadmill test uninterpretable, also constituted a noninclusion criterion.

All concomitant treatments with vasodilators and/or antiischemics, as defined in the French Vidal drug dictionary, were suspended. Treatments for hypertension or heart failure had to have been prescribed for at least three months and had to be stable.

The treadmill walking test was performed under standardized conditions: speed: 3.2 kph, slope: 10%, constant room temperature, at the same time of day and by the same investigator. Patients were not informed of the measuring time or the distance they were able to walk.

A radiometer was used to measure the $TcPo_2$. A probe 1 cm in diameter and 0.5 cm thick was used for the transcutaneous measurement: the low oxygen consumption measured increased the sensitivity of the examination. The probe attached to the skin consisted of a heating resistance connected to a thermostat, which maintained an optimal temperature of 44° C. The hyperemia induced in this way also increased the sensitivity of the measurement. The transcutaneous oximetry was recorded continuously in the two limbs in order to evaluate variations in $TcPo_2$ at rest, in the dorsal supine position, after stabilization, requiring about fifteen minutes; during exercise, up until onset of pain requiring the patient to stop walking, defining the absolute claudication distance, taken as the reference claudication distance at D 0 and D 30; and after exercise, in the supine position until recovery of a stable $TcPo_2$ lasting more than two minutes.

Statistics

All the results are expressed as mean ± SD (standard deviation). Statistical comparisons for continuous variables were achieved by using one-way

Downloaded from ang.sagepub.com at University of British Columbia Library on November 23, 2014

analysis of variance of change from baseline (difference between day 30 and day 0). For categorical variables, Pearson chi-square and Fischer's exact test were used.

Results

Study Population

On inclusion, there was no significant difference between the two groups in terms of the descriptive variables: sex, age, weight, height, history of disease, risk factors (smoking, diabetes, dyslipidemia, hypertension, physical activity) or the evaluation criteria: $TcPo_2$ and functional impairment.

Course of $TcPo_2$

At rest and after exercise, the $TcPo_2$ measurements did not vary significantly (Table I), which was only to be expected in patients with stage II arterial disease.

A reduction in the area of ischemia was observed in the EGb 761 group, reflecting an improvement in the local microcirculation, while this area of ischemia remained stable in the placebo group. In a comparison of the differences before and after treatment (Figure 1), the areas of ischemia decreased by 38% in the EGb 761 group but remained essentially stable (+5%) in the placebo group. This difference between groups is significant ($F[1.18]=4.91$; $P=0.04$) and the 95% confidence interval for the difference ranges from 0.89 to 3.87.

Table I

Course of $TcPo_2$ and Functional Impairment

	D0 m±sd	D30 m±sd	P Value
EGb 761 $TcPo_2$ (mm Hg) at rest	58.1±11.3	51.2±10.6	
			0.43
Placebo $TcPo_2$ (mm Hg) at rest	56.6±10.2	53.2±7.9	
EGb 761 $TcPo_2$ (mm Hg) after exercise	23.1±19.0	21.9±15.9	
			0.21
Placebo $TcPo_2$ (mm Hg) after exercise	21.5±21.6	29.4±15.9	
EGb 761 (mm) functional impairment	64.4±14.0	62.2±16.0	
			0.66
Placebo (mm) functional impairment	58.2±15.5	54.3±14.5	

Downloaded from ang.sagepub.com at University of British Columbia Library on November 23, 2014

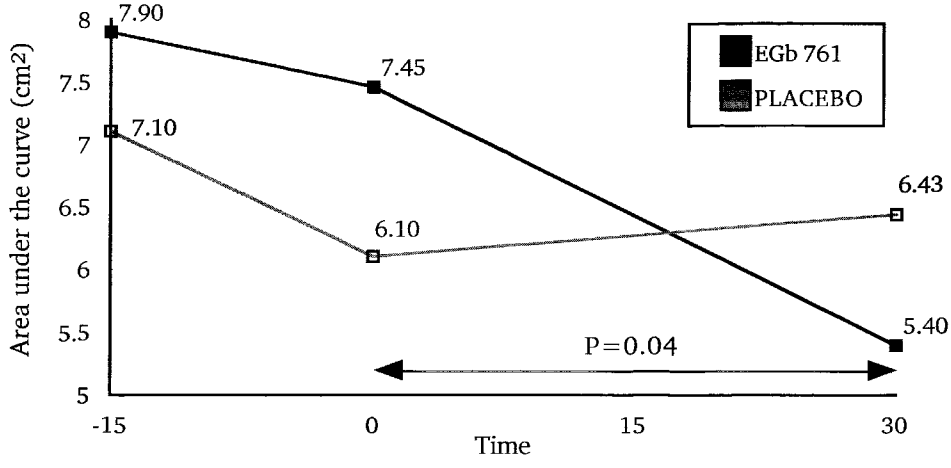

Figure 1. Course of area under the curve of $TcPo_2$ (cm^2, day).

Course of Functional Impairment

The functional impairment, evaluated by the patient by means of a 100 mm visual analogue scale, was not significantly modified (Table I) in either of the two groups over this brief treatment period (one month).

Discussion

The major contribution of $TcPo_2$ in this study was that it constituted an objective evaluation criterion of ischemia. $TcPo_2$ provides a good estimation of local perfusion under constant oxygen blood concentration. Conversely, any variation in $TcPo_2$ (eg, respiratory distress, hemoglobin level disturbance) may lead to modification of the $TcPo_2$ measurement independently of local microcirculation disorder. For this reason, patients with respiratory disorders or hemoglobin level disturbance were excluded.

In a previous study, this examination demonstrated, in about 100 patients with intermittent claudication, a postexercise fall in $TcPo_2$ greater than or equal to 10 mm Hg following a maximal walking test and a good correlation between the area under the curve and the severity of ischemia.[3] This study confirmed the rapid antiischemic action of EGb 761, reflected by a reduction in the area under the curve by the first month of treatment.

The improvement in planimetry was significantly greater in the group treated with EGb 761 than in the placebo group ($F\ [1.18]=4.91$; $P=0.04$). This improvement may correspond to a triple benefit: hemodynamic, hemorheologic, and metabolic. The actions contributing to the antiischemic effect can be explained by the various pharmacologic properties of EGb 761. EGb 761 exerts its vasoregulatory action on the entire vasculature;[4] in particular, it is able to relieve arteriolar spasm.[5,6] In terms of hemorheologic factors, EGb 761 counteracts platelet and erythrocyte hyperaggregability[7,8] (antisludge effect), and in the tissues, EGb 761 allows better glucose[9] and oxygen uptake under ischemic conditions, thereby stimulating aerobic glycolysis and promoting clearance of lactate. EGb 761 has also been demonstrated to be a potent scavenger of free radicals,[10,11] highly reactive molecules released during phases of ischemia-reperfusion.

Clinically, EGb 761 has demonstrated its efficacy in stage II peripheral arterial occlusive disease versus placebo in the long term, in particular by means of a three-year study[12] and versus reference drugs.[13,14] Its good acceptability increases the success rate of treatment in patients with arterial disease, who often suffer from other diseases (particularly diabetes) and who are poorly compliant.

Downloaded from ang.sagepub.com at University of British Columbia Library on November 23, 2014

Conclusion

Measurement of $TcPo_2$ during exercise constitutes a reliable and noninvasive criterion for the evaluation of tissue ischemia. This technique is of particular value in the follow-up of medical treatment of arterial disease, for it is able to evaluate the ischemic defect and its course. This double-blind, placebo-controlled study confirmed significantly ($F[1.18]=4.91$; $P=0.04$) the rapid antiischemic action of EGb 761 and its value in the management of peripheral arterial occlusive disease at the stage of intermittent claudication.

X. Mouren, M.D.
3 Place des Vosges
75004 Paris, France

References

1. Grard C, Desmhytterre J, Vinckier L, et al: Intérêt de l'oxymétrie transcutanée dynamique étagée dans l'artérite des membres inférieurs de stade II. Arch Mal Coeur 83:51-57, 1990.
2. Bauer U: L'extrait de Ginkgo Biloba dans le traitement de l'artériopathie des membres inférieurs: Étude sur 65 semaines. Presse Med 15:1546-1549, 1986.
3. Caillard P, Mouren X, Pujade B, et al: Objectifying exercise ischemia in peripheral vascular disease. Angiology 41:469-478, 1990.
4. Auguet M, Delaflotte S, Hellegouarch A, et al: Bases pharmacologiques de l'impact vasculaire de l'extrait de Ginkgo biloba. Presse Med 15:1524-1528, 1986.
5. Reuse-Blom S, Drieu K: Wirkung von Rökan auf den arteriolenspasmus beim kaninchen. In: Rokan Ginkgo Biloba Egb 761, ed. by Kemper FH, Schmid-Schonbein H. Berlin (Allemagne) Springer-Verlag, pp 69–73, 1991.
6. Delaflotte S, Auguet M, Defeudis FV, et al: Endothelium-dependent relaxations of rabbit isolated aorta produced by carbachol and by Ginkgo biloba extract. Biomed Biochem Acta 43: S212-S216, 1984.
7. Ernst E, Matrai A: Hemorheologische in vitro efferte von ginkgo biloba. Herz Kreisl 18:358-360, 1986.
8. Jung F, Mrowietz C, Kiesewetter H, et al: Effect of Ginkgo biloba on fluidity of blood and peripheral microcirculation in volunteers. Arzneim Forsch Drug Res 40:589-593, 1990.
9. Rapin JR, Le Poncin-Lafitte M: Consommation cérébrale du glucose. Effet de l'extrait de Ginkgo biloba. Presse Med 15:1494-1497, 1986.
10. Pincemail J, Deby C: Propriétés anti-radicalaires de l'extrait de Ginkgo biloba. Presse Med 15:1475-1479, 1986.
11. De Feudis FV: Ginkgo biloba extract (EGb 761): Pharmacological Activities and Clinical Applications. Paris: Eds Elsevier, 1991, pp 51–54.
12. Bauer U: Langzeibehandlung der peripheren arteriellen verschlusskrankheit mit Ginkgo biloba extrakt (GBE); eine 3-jahresuntersuchung. Vasa (suppl 15), 1986.
13. Bohmer D, Kalinski S, Michaelis P, et al: Behandlung der PAVK mit Ginkgo biloba extrakt (GBE) oder pentoxifyllin. Herz Kreisl 20:5-8, 1988.
14. Berndt ED, Kramar N: Medikamentose therapie der peripheren arteriellen verschlubkrankheit im stadium IIb eine bizentrische vergleichsstudie zwischen ginkgo biloba extrakt und buflomedil hydrochlorid. Therapiewoche 37:2815-2819, 1987.

Downloaded from ang.sagepub.com at University of British Columbia Library on November 23, 2014