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Effect of oral administration of high-dose nitric oxide donor L-arginine in men with organic erectile dysfunction: results of a double-blind, randomized, placebo-controlled study

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Objectives To determine, in a prospective randomized, double-blind placebo-controlled study, the effect of 6 weeks of high-dose (5 g/day) orally administered nitric oxide (NO) donor L-arginine on men with organic erectile dysfunction (ED).

Patients and methods The study included 50 men with confirmed organic ED who were randomized after a 2-week placebo run-in period to receive L-arginine or placebo. A detailed medical and sexual history, O'Leary's questionnaire, a specially designed sexual function questionnaire and a sexual activity diary were obtained for each patient. All participants underwent a complete physical examination including an assessment of bulbocavernosus reflex and penile haemodynamics. Plasma and urine nitrite and nitrate (designated NO_x), both stable metabolites of nitric oxide, were determined at the end of the placebo run-in period, and after 3 and 6 weeks.

Results Nine of 29 (31%) patients taking L-arginine and two of 17 controls reported a significant subjective improvement in sexual function. All objective variables assessed remained unchanged. All nine patients treated with L-arginine and who had subjectively improved sexual performance had had an initially low urinary NO_x, and this level had doubled at the end of the study.

Conclusions Oral administration of L-arginine in high doses seems to cause significant subjective improvement in sexual function in men with organic ED only if they have decreased NO_x excretion or production. The haemodynamics of the corpus cavernosum were not affected by oral L-arginine at the dosage used.

Keywords Erectile dysfunction, nitric oxide donor, L-arginine, oral treatment

Introduction

Nitric oxide (NO) is considered to be a principal mediator of penile erection, acting both as a neurotransmitter released in the nonadrenergic, noncholinergic (NANC) nerve terminals of the penis and as a vasodilator of the smooth muscle of penile arteries, sinusoids and trabeculae [1–4]. NO is derived from the terminal guanidine group of L-arginine by nitric oxide synthase (NOS) which converts the amino acid L-arginine to NO through oxidation of the guanidium nitrogen [2–5]. In this way, NO stimulates guanylate cyclase by acting as its physiological receptor in vascular smooth muscle cells, resulting in relaxation and vasodilatation [1–6]. In neuronal interactions, NO stimulates the increase in intracellular production of the second messenger molecule cGMP. NO binds to the iron in the haem moiety of guanylate cyclase and activates the guanylate cyclase, which then catalyses the formation of cGMP from 5′-guanosine triphosphate (GTP) [3–6]. This stimulation affects physiological processes, e.g. in the control of vascular tone, platelet inhibition and neurotransmission [1].

Animal and human studies have provided evidence that direct application of an NO donor or its substrate, e.g. L-arginine, causes relaxation of isolated corpus cavernosal tissue [3,7,8]. Furthermore, *in vivo* and *in vitro* studies showed penile erection after the activation of the L-arginine/NO pathway [9] in which the intracavernosal injection of linsidomine chlorohydrate (SIN-1), an NO donor, caused adequate erection in patients with ED [9–12].

In a short-term human pilot study on a few patients with mixed (i.e. psychogenic and/or organic) aetiology, oral supplementation with L-arginine showed positive results [13,14]. The present study was designed to

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determine in a controlled study whether the oral administration of a high dose of L-arginine would be effective for men with proven organic ED.

Patients and methods

This prospective, randomized, double-blind, placebo-controlled study included 50 of 75 patients (aged 55–75 years) with confirmed organic ED of >6 months' duration, who were unable to achieve adequate erection and rigidity sufficient for vaginal penetration and completion of successful intercourse after spontaneous sexual stimulation. All patients were recruited from our ED outpatient clinic; all study participants were either married or had stable heterosexual partners, and were men who were willing to improve their sexual function and agreed to cooperate in the protocol of all periodic follow-up assessments. Patients with severe cardiovascular diseases, cerebrovascular accident, uncontrolled hypertension, renal failure, hepatic insufficiency, endocrine abnormalities, psychiatric disorders, and evidence of dementia within 6 months or before the study onset were excluded. Patients were excluded if they were currently or recently treated for their ED with a constriction ring, external vacuum devices, intracorporeal injection of vasoactive drugs, intraurethral application of vasoactive medications or had undergone prosthetic or reconstructive surgery on the penis before inclusion in the study. The study was approved by the Ethics Committee on Human Experimentation in accordance with the standards of the Helsinki Declaration of 1975 as revised in 1983, and written consent was obtained from each participant.

The distribution of the patients by the diagnosis associated with the ED is given in Table 1. Before entering the study, a detailed medical and sexual history was obtained from all participants. The studied patients underwent a complete physical examination, including examination of the bulbocavernosus reflex and a penile haemodynamic study which included peak systolic velocity, end diastolic velocity and resistance index. All participants completed the questionnaire introduced in 1995 by O'Leary *et al.* [15], which contains 11 questions addressing the topics of sexual drive, erectile function, problem assessment and overall sexual satisfaction. An additional sexual function questionnaire specially designed by the authors addressed the number of erections, the quality of erections, libido and sexual performance (total number of attempts, number of successful attempts) as reported by the participants. Finally, all participants were asked to keep a sexual activity diary during the study period.

Table 1 Distribution of the study participants by diagnosis associated with erectile dysfunction

	Group		
Diagnosis	*L-arginine*	*Placebo*	*Total*
Diabetes mellitus	6	5	11
Arteriogenic	17	7	24
Veno-occlusive	2	0	2
Mixed vasculogenic	4	5	9
Neurogenic	1	0	1
Miscellaneous	2	1	3

The first 2 weeks of the study were a single-blind placebo run-in phase; at the end of this period, the patients were randomized to receive L-arginine or placebo therapy which lasted for 6 weeks. Identical capsules of L-arginine monohydrochloride (Ajinomoto Co., Kawasaki, Japan) and placebo were used. The daily 5 g dose of L-arginine or placebo was divided and given in three doses. The medication was encapsulated by the Droret Co., Israel, and randomization, registration and medication supply were controlled by the hospital pharmaceutical department. Physical examination and measurement of clinical variables, including duplex Doppler ultrasonography, were performed by one investigator (J.C.); patients were assessed 14 days before and at 0, 14, 35, and 42 days after treatment commenced. Plasma and urine NO_2 and NO_3, stable metabolites of NO (designated NO_x), were determined before randomization and after 3 and 6 weeks of therapy, as previously described [16].

The results from both groups were analysed statistically, with the mean (SEM) and Student's *t*-test (paired or unpaired as appropriate) used for statistical comparison. The chi-square test was used for continuous and discrete variables, with $P<0.05$ considered to indicate significance.

Results

Of the 50 original participants, 32 were assigned to L-arginine treatment and 18 to placebo (controls). Four patients withdrew from the study; three in the L-arginine group refused to continue treatment because of lack of effect in the placebo run-in phase, and one in the placebo group because of palpitations. Thus, the compliance was >90% in both treatment arms. At the end of the study, nine of 29 (31%) men treated with L-arginine but only two of 17 treated with placebo reported a significant improvement in sexual function in their diaries. All objective variables remained unchanged in both groups (Table 2). Baseline values of the subjective responders among the men treated with L-arginine (nine) were compared with those of all 37 participants not

Table 2 Comparison of the measured variables between the L-arginine group and controls at the beginning and end of the study. None of the differences were significant

Mean (SEM) variable*	Group			
	L-arginine		Placebo	
	Initial†	End	Initial	End
Scores				
O'Leary	18.6 (1.3)	17.7 (1.4)	19.2 (1.7)	19.8 (1.9)
Sexual function	8.5 (1.0)	9.3 (1.2)	9.2 (1.6)	9.2 (1.7)
Sexual diary	0.7 (0.2)	4.6 (0.7)	0.9 (0.2)	4.2 (0.8)
PSV	1185 (78)	1579 (169)	1341 (153)	1290 (9.8)
EDV	640.8 (40)	844.3 (81)	730.9 (84)	694.9 (52)
RI	0.5 (0.01)	0.5 (0.01)	0.5 (0.03)	0.5 (0.01)

*PSV, Peak systolic velocity. EDV, End diastolic velocity. RI, Resistance index. †End of the 2 week run-in placebo period.

Table 3 Comparison between those subjectively improved (nine) and the other 20 men in the L-arginine group at baseline and after treatment. None of the differences were significant

Mean (SEM) variable	Day 0		Day 60	
	Improved	Other	Improved	Other
Scores				
O'Leary	20.1 (3.0)	18.0 (1.7)	20.4 (2.9)	16.5 (1.5)
Sexual function	9.2 (1.5)	8.2 (1.0)	10.2 (1.7)	8.1 (0.9)
Sexual diary	1.1 (1.4)	0.6 (0.2)	1.3 (0.6)	2.0 (0.6)
PSV	1220 (136)	1171 (100)	1570 (124)	1583 (241)
EDV	674 (67)	628 (50)	851 (66)	841 (115)
RI	0.5 (0.04)	0.5 (0.01)	0.5 (0.01)	0.45 (0.01)

*PSV, Peak systolic velocity. EDV, End diastolic velocity. RI, Resistance index.

responding. There was no significant difference in any of these variables. A comparison between the subjectively improved nine men with the other 20 men in the L-arginine group also yielded no significant difference (Table 3). The changes in plasma and urine NO_x are give in Table 4; the administration of L-arginine resulted in a significant increase in both. The initial urinary NO_x level in the nine men treated with L-arginine who had a subjective improvement in their sexual activities was significantly lower than that of the other patients and this level had doubled at the end of the study.

The patients tolerated the high-dose of L-arginine hydrochloride well and there were no significant side-effects. The decrease of systolic and/or diastolic blood pressure was about 10%, causing no systemic effect and required no interruption of the study for any patient. The fluctuation in heart rate was not significant; the one patient who withdrew from the study because of palpitations was in the control group. Although discomfort such as nausea, vomiting, diarrhoea, headache, flushing and numbness after the administration of L-arginine has been reported [17], none of the present patients reported such complaints.

Table 4 Plasma and urinary NO_x in the various groups

Group	Mean (SEM) NO_x*		
	Initial (end of placebo)	After	
		3 weeks	6 weeks
Placebo			
Plasma	43.3 (5.0)	44.1 (3.8)	44.3 (5.2)
Urinary	11.7 (1.8)	12.5 (5.0)	13.1 (1.6)
L-arginine			
All			
Plasma	38.9 (3.9)	46.3 (6.1)†	40.1 (2.6)
Urinary	9.5 (1.3)	13.1 (2.1)†	13.8 (2.6)†
Nonresponders			
Plasma	40.1 (4.2)	40.4 (5.8)	37.6 (8.5)
Urinary	10.1 (1.4)	11.7 (1.7)†	10.5 (1.8)
Responders			
Plasma	36.5 (7.1)	51.3 (10.1)†	44.4 (6.5)†
Urinary	6.8 (2.3)‡	14.5 (3.5)	14.4 (3.3)†

*Plasma NO_x in μmol/L; urinary NO_x in μmol/L per mg creatinine (initial) value. †$P < 0.01$ vs the L-arginine responders. ‡$P < 0.05$ vs placebo and L-arginine nonresponders.

Discussion

Oral drug administration is the easiest and most acceptable treatment for ED compared with other successful modalities, e.g. external vacuum devices, topical creams, intracavernosal injection and intraurethral application of vasoactive drugs, and different penile reconstructive vascular and prosthetic surgical techniques developed in the last three decades [13,14,18,19]. Until recently, yohimbine hydrochloride was the most widely used oral medication for ED, but the outcome was disappointing, even when it was used in high doses [18]. The results of clinical studies on a selective 5-phosphodiesterase inhibitor are promising, but await long-term assessment [19,20].

L-arginine, an NO donor, is a basic component of the daily diet which may increase NOS activity and may affect penile erection [13,14,21]. Recent experimental and clinical investigations show that NO, a NANC neurotransmitter that is released at nerve ends and activated at the endothelium of penile arteries, sinusoids and trabeculae of cavernosal smooth muscle, is responsible for smooth muscle relaxation and penile erection [2–4,6–8]. Despite general agreement of the importance of NO in penile erection, we are aware of the results of only one reported short-term pilot clinical observation of L-arginine [14]. These authors studied the effect of the oral administration of L-arginine in a few patients with combined psychological and organic ED. The promising results of this study were based on a subjective self-assessment by the participants.

The present study included only patients with confirmed organic ED; patients with psychogenic ED were excluded. We recognize that there is a secondary psychological effect of ED which may have an impact on the definitive diagnosis even in what appears to be a highly selected group of men with evident organic disease. However, an emotional burden invariably accompanies this and other dysfunctions, and we think that the overriding organic problem should define the fundamental diagnosis as the cause of ED. Six weeks of L-arginine therapy was associated with no significant improvement in the objective variables assessed. A fixed dose of L-arginine was used (5 g/day in 10 capsules), considering the participants' capability for complying with medication and that 5 g/day is almost threefold higher ($\approx$0.07 mg/kg) than that used in other human studies for other purposes (1.4–2.5 g/day) [14,20–22]. Moreover, this dose is 0.02–0.03 mg/kg for a man of average size (70 kg), so that if it did have pharmaceutical potential, this amount should be sufficient for the effective treatment of patients with organic ED.

A third of the present patients treated with L-arginine reported a significant subjective improvement in their sexual function; this seems to confirm the results of Zorgnotti and Lizza [14]. The subjective improvement in this subgroup of patients, not accompanied by changes in the objective variables assessed, suggests that L-arginine therapy may be especially beneficial in patients with a low baseline NO production. The plasma and urinary NO_x levels were no different between the groups at baseline (at the end of the placebo run-in period). The administration of L-arginine resulted in a significantly higher urinary NO_x level than the pretreatment values in all treated patients. Interestingly, dividing the L-arginine group into those subjectively improved and unimproved, there were differences in their NO system. The nine responders had lower urinary NO_x levels before therapy and showed greatly increased plasma and urinary NO_x after treatment.

Because NO has been recognized as a vasodilator of the smooth muscle of penile arteries, sinusoids and trabeculae [1–6], our expectation was that an NO supplement might improve intracavernosal haemodynamic variables. We are aware of no published reports on oral or intravenous administration of L-arginine causing haemodynamic changes in the corpus cavernosal circulation. There was no statistically significant improvement of any of the measured haemodynamic variables at any point of the study. This can be explained by an insufficient intracavernosal concentration of L-arginine, or perhaps by a lack of delivery of L-arginine to the corpus cavernosum when administered orally. It remains to be established if higher doses of L-arginine or a more prolonged period of treatment would be more effective in patients with ED who show no evidence of low NO production.

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