EXPERIMENTAL METHODS FOR CLINICAL PRACTICE

Study of the Correlation between Clinical Efficiency of Impaza and Serum ADMA Level

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 145, No. 3, pp. 342-344, March, 2008
Original article submitted January 16, 2008

Correlation between superlow-dose antibodies to endothelial NO synthase (Impaza) and serum level of ADMA was evaluated in a double blind placebo-controlled study. The reduction of ADMA in patients with erectile dysfunction after impaza treatment was paralleled by improvement of clinical symptoms. No clear-cut correlation between ADMA level and impaza effect was detected.

Key Words: *erectile dysfunction; superlow-dose antibodies to endothelial NO synthase; ADMA*

Erectile dysfunction (ED) is a multifactorial chronic disease of complex etiology; one of its causes is endothelial dysfunction [5] characterized by impairment of homeostasis between vasodilating and vasoconstrictor factors [8]. Impairment of NO synthesis, reduction of NO bioavailability as a result of its reduced production in the presence of low endothelial NO synthase (eNOS) activity are among the key pathological mechanisms of endothelial and erectile dysfunction development [3,8]. Recent findings indicate that poor activity of eNOS is explained by high blood concentration of endogenous eNOS competitive inhibitor, asymmetrical dimethyl-L-arginine (ADMA) [1,6]. ADMA is a guanidine-substituted L-arginine analog, but there is no data indicating ADMA formation directly from free L-arginine. ADMA forms as a result of posttranslation protein methylation and their subsequent hydrolysis [7]. About 300 μmol ADMA forms daily in humans, 250 μmol is metabolized by dimethylarginine dimethylaminohydrolase [1,7]. The effect of ADMA on eNOS activity was noted in some diseases (diabetes, renal insufficiency, cardiovascular diseases). Changed concentration of ADMA can serve as an additional factor provoking the development of ED [8].

The results of preclinical and clinical studies of impaza, a preparation containing superlow-dose antibodies to endothelial NO synthase (C12+C30+C200), indicate that this preparation can restore the erectile function [4]. It was shown that drug injection led to an increase in the content of cyclic guanosine monophosphate (cGMP) in cavernous bodies at the expense of recovery of adequate production of NO in tissues [2].

We studied the relationship between clinical efficiency of impaza and changes in ADMA level.

MATERIALS AND METHODS

Double blind 12-week placebo-controlled study was carried out in 60 patients (30 in impaza and 30 in placebo groups) with mild or medium severe ED (the erectile function score 10-25 points according to the International score of erectile function, ISEF) and 17 healthy volunteers without ED (control group). The mean age of patients in the

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0007-4888/08/1453-0367

impaza and placebo groups was 45.1±2.8 and 50.7± 2.0 years, respectively, the duration of ED 4.6±0.7 and 4.2±0.5 years, respectively, and erectile function score 16.4±0.8 and 16.5±0.8 points, respectively.

The patients received one tablet of impaza every other day and one more tablet additionally (if needed) 1 h before sex.

Clinical efficiency of therapy was evaluated 4 and 12 weeks after the beginning of impaza treatment by the time course of the parameters listed in the iSEF questionnaire (erectile function, satisfaction with coitus, orgasm, libido, total satisfaction), subjective opinion of the patient, and conclusion of the physician. "Excellent effect" implied a more than 50% increase in the "erectile function" value or the score of >25 points, "good effect" corresponded to a 30-50% increase of the parameter, "satisfactory effect" was a 10-30% improvement, "no effect" corresponded to a 10% increase, and "deterioration" indicated a 10% or more reduction of the parameter.

The effect of impaza on serum concentration of ADMA was evaluated twice in the impaza and placebo groups (before and after 12-week treatment) and once in the control group. Blood ADMA level was measured by ELISA (CardioS Vasics-Medical Science Labs).

RESULTS

A negative correlation between serum ADMA concentration and erectile function ISEF index (r= -0.81) was detected in the control group (Fig. 1). This correlation indicates an important role of ADMA in normal regulation of erectile function.

The drug therapy during 12 weeks led to a significant reduction of the erectile function index (Table 1). The integrative index of erectile function increased by 3 points and more in 90% patients treated with impaza. Impaza efficiency was evaluated as excellent and good by 66.7% patients in the impaza group, *vs.* just 16.6% in the placebo group.

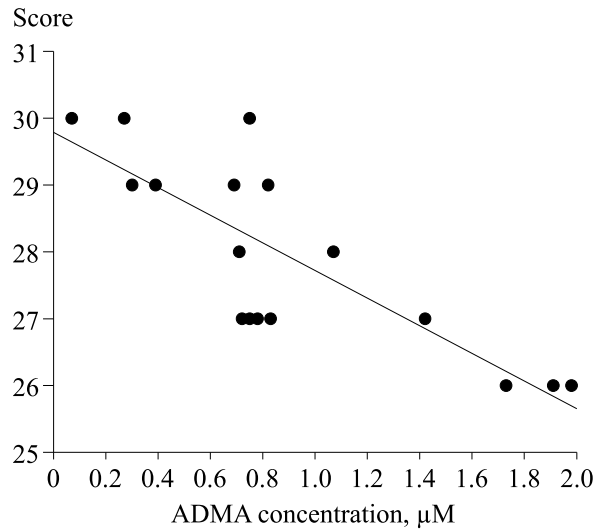

Fig. 1. Time course of serum ADMA level and the erectile function ISEF index.

No pronounced or statistically significant changes in ADMA concentration were detected by the end of therapeutic course in the impaza and in placebo groups (Table 2).

A relationship between the time course of clinical shifts in ED during treatment and ADMA level was detected. The patients were divided into 2 subgroups by the results of analysis of relationship between ADMA concentration and treatment efficiency: one subgroup consisted of patients with ADMA level reduction and the other with its increase. A total of 81.25% patients of the impaza subgroup with reduction of ADMA level evaluated the treatment efficiency as excellent or good, *vs.* just 16.67% in the placebo group, and 50% patients in the impaza subgroup with ADMA level increase evaluated the results as excellent or good, *vs.* 18.18% in the placebo group (Table 3).

TABLE 1. Drug Efficiency after 12-Week Treatment ($M\pm m$)

Parameter	Impaza	Placebo
Number of patients	30	30
Initial EF, score	16.4±0.8	16.5±0.8
EF during week 12, score	22.4±1.0*	17.5±1.0
EF increment by week 12, score	6.00±0.73*	1.00±0.78
Patients with EF score >25 at week 12, %	36.7 (21.9-54.5)	10 (3.5-25.6)
Patients with EF increment of at least 3 points, %	90 (74.4-96.5)	20 (9.5-37.3)
Patients with EF improvement or recovery, %	90 (74.4-96.5)	23.3 (11.8-40.9)
Patients evaluating the effect as excellent and good, %	66.7 (48.8-80.8)	16.6 (7.3-33.6)

Note. EF: erectile function. The 95% confidence interval is shown in parentheses. *p<0.01 *vs.* placebo.

TABLE 2. Serum ADMA Levels (μM) in Patients (*M*±*m*)

Group	Initial	After 12 weeks	Initial value D, %
Control (*n*=17)	0.89±0.14	—	
Impaza (*n*=30)	0.75±0.08	0.77±0.04	2.6
Placebo (*n*=30)	0.80±0.07	0.81±0.10	1.25

TABLE 3. Relationship between the Dynamics of ADMA Level and Clinical Efficiency (*M*±*m*)

Group, parameter	Patients with ADMA increase *vs.* initial level	Patients with ADMA decrease *vs.* initial level
Impaza		
Number of patients	14	16
Age (years)	38.29±4.11	51.13±3.28
ED duration (years)	3.46±0.73	5.80±1.13
Patient's evaluation of efficiency after 12 weeks, %		
"excellent" or "good"	50.00	81.25
no effect	14.29	6.25
deterioration	14.29	0.00
Physician's evaluation of efficiency after 12 weeks, %		
EF>25	28.57	50.00
EF increment by 3 points	42.86	50.00
no effect	28.57	0.00
Placebo		
Number of patients	11	19
Age (years)	55.82±3.18	47.79±2.46
ED duration (years)	5.86±1.12	8.29±3.52
Patient's evaluation of efficiency after 12 weeks, %		
"excellent" or "good"	18.18	16.67
no effect	54.55	66.67
deterioration	27.27	11.11
Physician's evaluation of efficiency after 12 weeks, %		
EF>25	9.09	16.67
EF increment by 3 points	9.09	5.56
no effect	81.82	77.78

ADMA concentrations increased from 0.49±0.09 to 0.78±0.05 ($p<0.01$) in 14 impaza group patients and decreased from 0.98±0.10 to 0.76± 0.06 ($p<0.01$) in 16 patients. Eleven placebo group patients developed an increase of this parameter from 0.550±0.005 to 1.09±0.23 ($p<0.05$) and 19 demonstrated a decrease from 0.94±0.09 to 0.64± 0.07 ($p<0.001$).

Analysis of the relationship between impaza and placebo efficiency and changes in ADMA concentrations after 12-week treatment of patients with ED failed to detect a clear-cut correlation between these two parameters, presumably because of involvement of NO-dependent and non-NO-dependent processes in the maintenance of erectile function [5,8]. In addition, despite an increase in the blood ADMA concentrations observed in many diseases, it is unknown whether the concentration of endogenous ADMA reaches the values sufficient for suppressing NO production. Except for renal insufficiency, there are no proofs that an increase in the blood ADMA level can cause the disease [1].

We conclude that ED is not always linked with an increase of the blood ADMA level, despite a clear-cut correlation of erectile function with ADMA concentration in subjects without ED.

Hence, reduction of ADMA level in patients with ED treated with impaza is associated with positive clinical efficiency of the drug, though no

clear-cut correlation between ADMA level and drug efficiency was detected, as ED is a multifactorial disease and endothelial dysfunction is one of its causes.

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