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VASCULAR DEMENTIA ITALIAN SULODEXIDE STUDY (VA.D.I.S.S.) CLINICAL AND BIOLOGICAL RESULTS.

Lucilla Parnetti[1], Daniela Mari[2], Giuseppe Abate[3], Roberto Balestreri[4], Domenico Cucinotta[5], Raffaella Coppola[2], Antonio Cherubini[1], Patrizio Ferrari[6], Umberto Senin[1]

[1]Section of Gerontology and Geriatrics, Perugia University; [2]Angelo Bianchi Bonomi Hemophilia and Thrombosis Center IRCCS, Maggiore Hospital and University, Milano; [3]Chair of Geriatrics, Chieti University; [4]Chair of Geriatrics, Genova University; [5]III Department of Geriatrics, M.Malpighi Hospital, Bologna; [6]Alfa Wassermann, Bologna

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Abstract In order to evaluate the biological effects on some haemostasis factors of antithrombotic-hemorheological treatments on patients with vascular dementia, a multicenter, randomized, double-blind, double-dummy, study comparing sulodexide (Sdx, 50 mg bid orally for 6 months) and pentoxifylline (Ptx, 400 mg tid orally for six months) was carried out. Eighty-six patients, 46 in Sdx group, 40 in Ptx group, fulfilling the NINDS-AIREN criteria for probable vascular dementia were evaluated. Plasma fibrinogen levels showed a significant reduction in both groups, in patients with high basal levels (≥350 mg/dl), the reduction being earlier in Sdx group (2nd month of therapy) than in Ptx group (4th month of therapy). In Sdx group a significant reduction in factor VII-Ag (baseline 102.8 U/dl; 6th month 90.1 U/dl) was also observed. Both drugs induced a slight reduction in activated factor VII levels as well. A parallel improvement of G.B.S. Rating Scale for dementia scores was observed in Sdx group. These results seem to indicate that sulodexide treatment can have positive effects in vascular dementia.

Key words: vascular dementia, sulodexide, pentoxifylline, fibrinogen, haemostasis factors.
Corresponding author: Lucilla Parnetti, MD, PhD, Gerontologia e Geriatria, Università di Perugia, via Eugubina 42, 06122 Perugia, Italy.
Tel.:+39-74-5855822. Fax: +39-75-5730259. e-mail: parnetti@unipg.it

Vascular dementia (VaD) is a common cause of dementia in the elderly, accounting for at least 20% of all causes; its prevalence increases noticeably with advancing age surpassing prevalence rates of Alzheimer's Disease in subjects over 80 years of age (1). The conventional vascular risk factors explain only partially the causes of vascular dementia, a number of different mechanisms being possibly involved (2, 3).

On theorical ground there is a potential for the prevention and treatment of cerebrovascular diseases (4); to this purpose drugs interfering with hemostasis could be of interest. Although the actual role played by thrombotic disease in the development of VaD is still not completely known, abnormally elevated levels of some coagulation parameters have recently been described in this pathological condition (5). Specifically, high fibrinogen levels (≥ 350 mg/dl) represent a major vascular risk factor for cardiovascular diseases (6,7). No controlled trials dealing with treatment of VaD by means of drugs that affect hemostasis are available. A pilot study (8) with aspirin (325 mg daily for 3 years) gave promising results. The xantine derivative pentoxifylline has also been successfully used for treatment of elderly patients with vascular dementia (9); in two other series (10,11) this drug showed to be able to improve the haemorheological pattern (by decreasing blood viscosity and improving red blood cell deformability) parallel to a favourable trend of psychobehavioral scores in cognitively impaired old subjects. The use of anticoagulant therapy has also been proposed in senile and presenile dementia (12).

Sulodexide is a highly purified preparation containing a heparin fraction with a high affinity for antithrombin III (80%) and a dermatan fraction with affinity for heparin cofactor II (20%) (13). In vivo antiatherosclerotic effects of sulodexide (14,15) may be related to a hypolipidemic activity linked to lipoprotein-lipase release (16), confirmed by a reduction in plasma and serum viscosity, (17,18) a more rapid catabolism of cholesterol-rich lipoproteins by the liver (16) and an antiproliferative effect on smooth muscle cell types (14). Both in animals and in human beings sulodexide inhibits activated factor X without influencing the activated partial thromboplastin time and thrombin time (19-21). It also exerts a fibrinolytic activity, expressed by tissue-plasminogen activator inhibitor (t-PA) activation and plasminogen activator inhibitor (PAI-1) inhibition (17, 21-23). Recently pharmacological evidence of antiaggregant activity has been described, manifested as inhibition of leukocyte pathway of platelet aggregation (24). Clinical trials in peripheral obstructive arteriopathy (25,26) and prevention of myocardial reinfarction (27) have provided evidence of sulodexide efficacy in these conditions.

With the primary aim of evaluating the effect of antithrombotic therapies on some haemostatis factor in VaD patients, we carried out a multicentre double-blind study comparing sulodexide with pentoxifylline.

PATIENTS AND METHODS

Ninety-three elderly patients (37 males, 56 females, mean age 75±5, range: 65-80 years) were enrolled in the study in four italian geriatric centers. All of them fulfilled the NINDS-AIREN (28) diagnostic criteria for probable vascular dementia; a Mini Mental State Examination (MMSE) (29) score between 11 and 22 was used as inclusion criterion. They were not taking any medication interfering with platelet aggregation and/or coagulation; they did not suffer from TIA/stroke episodes in the last three months. Patients were randomly assigned to a six-month treatment with sulodexide (Sdx; 50 mg bid orally) or pentoxifylline (Ptx; 400 mg tid orally). According to high (≥ 350 mg/dl) or normal (<350 mg/dl) fibrinogen levels at baseline, patients were subdivided in two subgroups, expecting a reduction of at least 10% (or 40 mg/dl)

of fibrinogen levels in patients with high fibrinogen (primary aim).

Clinical parameters

Clinical efficacy was assessed by means of Gottfries-Bråne-Steen (GBS) Rating Scale for Dementia (30). It is composed of three subscales which give careful information on motor (GBS-m), intellectual (GBS-i) and emotional (GBS-e) disturbances; score for each subscale ranges from 0 (no impairment) to 6 (maximum impairment). The scale is widely used in several countries; in particular the italian version has shown an excellent inter-rater reliability (31). Since the primary aim of the study was to assess biological effects rather than clinical efficacy of Sulodexide in vascular dementia, we preferred to use this type of instrument - which gives substantial information on the general functional state of the patient - rather than single psychometric tests which give details of specific neuropsychological functions. GBS was administered at baseline, at the 4^{th} and 6^{th} month of therapy; at the end of treatment (t^6) MMSE was also repeated.

Biological parameters

Blood sampling: venous blood was obtained between 8:00 and 10:00 am from the antecubital veins by two syringe techniques using 19-gauge needles. All the coagulation and fibrinolysis assays were carried out on blood collected in sodium citrate at a final concentration of 3.8% (wt/vol). All plasma specimens were centrifuged at 4°C (except for activated factor VII, (FVIIa) at room temperature) for 20 minutes at 2,000 g and stored at -80° C until assayed within 2-3 months. All assays were done in Milan, Italy. Coagulation and fibrinolytic parameters were evaluated at baseline (t^0), after 2 (t^2), 4 (t^4) and 6 (t^6) months. FVIIa was measured only in a subset of 20 patients studied at one Centre (Perugia) at t^0 and t^6. Plasma fibrinogen was measured by a fibrin polymerization assay (Boehringer Biochemia). Factor VII antigen (FVII-Ag) plasma levels were measured with an ELISA that is not affected by FVII activation as previously described (32). Plasminogen activator inhibitor type 1 activity (PAI-1) was measured by a chromogenic method (Biopool, Umeå, Sweden). FVIIa was measured by a one-stage (33), prothrombin time-based assay using a truncated soluble form of recombinant tissue factor (kindly supplied by Dr. Y. Nemerson, Mount Sinai Hospital Medical School, New York, NY) that, upon relipidation, reacts with factor VIIa but not with one-chain factor VII.

RESULTS

A total number of 93 patients with probable VaD were randomized. Results refers to 86 patients (n. 46 in sulodexide group, n. 40 in pentoxyfilline group), after seven patients dropped out (see tolerability). In Table I details of the patients studied are reported. As far as age, sex, education and severity of cognitive impairment were concerned, no differences were detected between the two groups. As regards to vascular profile of the patients, the two groups showed similar distribution of major vascular risk factors, concomitant cardiovascular diseases and CT scan findings indicative of cerebrovascular disease. The majority of patients were affected by subcortical vascular dementia with small deep infarcts and leukoencephalopathy.

Clinical parameters

In Table II neuropsychological scores at different times of the study are reported. GBS scores showed a significant improvement only in the sulodexide group both at t^4 and t^6 ($p<0.01$ vs t^0). MMSE scores showed some positive but not relevant trend in both groups at the end of treatment.

TABLE I

Details of the Patients Enrolled (*Values are Given as Mean ± SEM)

	Sulodexide	Pentoxifylline	total
no. of patients enrolled	49	44	93
age: mean	75	76	75
range	65-80	66-80	65-80
sex: m/f	22/27	15/29	37/56
education: years of schooling	5.3	5.5	5.4
Hachinski ischemic score*	7.7 ± 0.1	7.9 ± 0.2	7.8 ± 0.1
M.M.S.E.*	17.6 ± 0.4	18.0 ± 0.4	17.8 ± 0.4
Major vascular risk factors	no. %	no. %	no. %
hypertension	44 (90)	35 (79)	79 (85)
diabetes mellitus	8 (16)	12 (27)	20 (21)
smoke habits	24 (49)	16 (36)	40 (43)
Cardiovascular diseases			
TIA/stroke episodes	34 (69)	34 (77)	68 (73)
myocardial infarction	2 (4)	3 (7)	5 (5)
angina pectoris	2 (4)	1 (2)	3 (3)
alteration of cardiac rhythm	10 (23)	9 (20)	19 (20)
peripheral vascular disease	8 (16)	5 (11)	13 (14)
Cerebral CT scan findings			
focal cortical lesions	20 (41)	16 (36)	36 (39)
focal subcortical lesions	30 (61)	31 (70)	61 (66)
diffuse subcortical lesions	22 (45)	24 (54)	46 (49)

TABLE II

Mean (± SEM) Neuropsychological Scores Observed in VaD Patients Treated with Sulodexide and Pentoxifylline at Baseline(t^0), at the Fourth (t^4) and Sixth (t^6) Month of Treatment

		t^0	t^4	t^6
MMSE	Sdx	17.6 ± 0.4	---	20 ± 0.6
	Ptx	18 ± 0.4	---	20 ± 0.4
G.B.S. Rating Scale				
motor impairment	Sdx	1.64 ± 0.14	1.58* ± 0.14	1.54* ± 0.16
	Ptx	1.59 ± 0.13	1.53 ± 0.14	1.46 ± 0.17
intellectual impairment	Sdx	2.06 ± 0.09	1.88* ± 0.09	1.79* ± 0.1
	Ptx	1.98 ± 0.08	1.95 ± 0.1	1.87 ± 0.12
emotional impairment	Sdx	2.1 ± 0.12	1.88* ± 0.12	1.76* ± 0.12
	Ptx	1.89 ± 0.1	1.9 ± 0.1	1.75 ± 0.11

Patients evaluated: 46 Sdx, 40 Ptx; * $p<0.01$ vs t^0 (Mann Whitney).

Biological parameters

In Table III fibrinogen, FVII-Ag, PAI-1 and FVIIa levels are reported. As regards fibrinogen levels, mean values did not differ between the two groups. Dividing patients in two subgroups according to normal (<350 mg/dl) or high fibrinogen levels (≥350 mg/dl) (Fig. 1) a significant reduction was observed in patients with higher levels; the decrease was earlier (t^2) in Sdx group compared to Ptx group (t^4). Both subgroups maintained these values until the end of treatments. A significant reduction in factor VII-Ag levels was observed at t^6 as compared to t^0 ($p<0.05$) only in sulodexide group. No significant variation of PAI-1 levels were observed in any group. Finally, FVIIa (evaluated in 10 patients treated with sulodexide and 10 with pentoxifylline) showed a slight trend toward a decrease in both groups. It should be noted that baseline levels of FVIIa were remarkably higher than reference values (3.1±1.1 ng/ml, $p<0.001$).

SAFETY AND TOLERABILITY

In sulodexide group 3 drop-outs due to melanoma, angina, heart failure were observed; two episodes of mild gastralgia -not requiring drug suspension- were also registered. In pentoxifylline group 3 drop-outs due to gastralgia (2 pts.) and asthenia were obtained; one case of headache and 3 cases of mild gastralgia did not require drug suspension. No abnormalities in routine haematological and haematochemical parameters were observed in any subject.

DISCUSSION

In Table IV the main results obtained in this 6 month clinical-biological trial carried out in vascular dementia patients treated either with sulodexide or pentoxifylline are summarized.

Both drugs are known to have antithrombotic and haemorheological properties; in this study they have confirmed to be able to reduce high fibrinogen levels, sulodexide disclosing also a positive effect on some hemostasis parameters, namely factor VII-Ag, and on functional parameters, as documented by GBS scores.

A slight trend toward a decrease of activated factor VII was observed in both treatment groups as well, although this finding is relative to a small subgroup of patients.

The existence of a strong association between high plasma fibrinogen levels and stroke (7,34), as well as the role of factor VII coagulant activity as major risk factor for cardiovascular events (35,36), is now well documented. Nevertheless, scanty is the knowledge of the actual relevance of altered hemostasis factors on pathophysiology of vascular dementia, as well as the impact of anti-thrombotic drugs on this condition.

In a recent investigation, hemostasis abnormalities similar to those found in patients with atherothrombotic diseases were observed in patients with vascular dementia (37), suggesting that these alterations can have a role in the pathogenesis of the disorder. In particular, high levels of activated Factor VII could be explained if we assume that vascular injury induces exposure of tissue factor thus accelerating formation of activated Factor VII/tissue factor pathway inhibitor (TFPI) complex. TFPI, a major inhibitor of activated Factor VII, is released in plasma by heparin and glycosaminoglycans (38), therefore, we might speculate that Sdx, a highly purified glicosaminoglycan preparation, by inducing a release of TFPI, influences Factor VII zymogen levels.

Few years ago vascular dementia has been defined as a form of preventable senility, being the last clinical step after the brain-at-risk stage and the pre-dementia stage (4). In this perspective aimed at preventing vascular dementia, one should consider to treat also patients who are in the stages preceding vascular dementia. Due to the potential clinical relevance of a successfull treatment of

TABLE III

Haemostasis Parameters Measured at Different Times of the Study

		pts n°	t^0	t^2	t^4	t^6
Fibrinogen	Sdx	49	346 ± 10	327 ± 10	320 ± 12	332 ± 14
(mg/dl)	Ptx	44	343 ± 12	345 ± 12	312 ± 10	322 ± 11
<350 mg/dl	*Sdx*	*22*	*288 ± 7*	*301 ± 9*	*289 ± 7*	*301 ± 13*
	Ptx	*21*	*291 ± 11*	*302 ± 13*	*291 ± 10*	*303 ± 17*
≥ 350 mg/dl	*Sdx*	*27*	*408 ± 9*	*355* ± 17*	*358* ±21*	*367* ± 23*
	Ptx	*23*	*394 ± 13*	*394 ± 13*	*340* ±17*	*344* ± 13*
Factor VII-Ag	Sdx	49	102.8 ± 4.3	99.1* ± 5.3	100.7 ± 4.8	90.1* ± 4.7
(U/dl)	Ptx	44	101.0 ± 4.7	104.0 ± 5.1	97.6 ± 4.7	89.6 ± 5.8
Plasminogen activator	Sdx	49	12.1 (10-17)	12.5 (9-18)	12.1 (11-16)	11.0 (8-15)
inhibitor type 1 (IU/ml)	Ptx	44	11.8 (9-16)	11.4 (10-15)	12.4 (10-18)	11.9 (10-14)
Actived factor VII	Sdx	10	4.4 ± 0.7	---	---	3.3 ± 0.7
(ng/ml)	Ptx	10	4.3 ± 0.7	---	---	3.1 ± 0.4

Fibrinogen, FVII antigen and FVIIa: means ± SEM
PAI-1: geometric means (95% confidence intervals)
* $p < 0.05$ t^0 vs all times (ANOVA, "t" test).

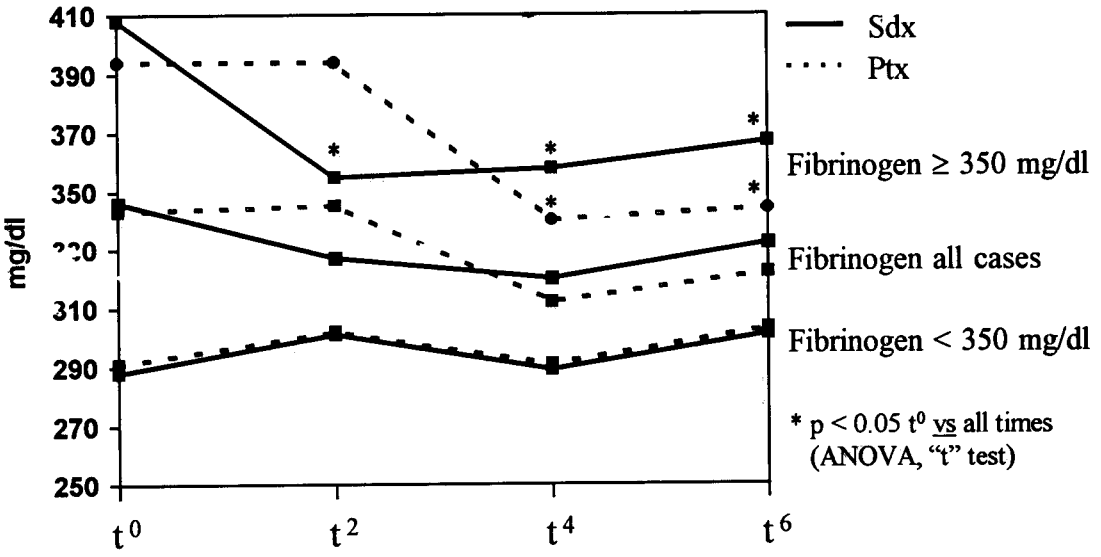

FIG. 1

Time Course of Mean Fibrinogen Levels

TABLE IV - Summary of Results Obtained

		Sulodexide	Pentoxifylline
Biological parameters	high fibrinogen (≥ 350 mg/dl)	⇓⇓*	⇓⇓**
	Factor VII-Ag.	⇓⇓	=
	activated Factor VII	=⇓	=⇓
	PAI-1	=	=
Clinical parameters	GBS motor impairment	⇓⇓	=
	intellectual impairment	⇓⇓	=
	emotional impairment	⇓⇓	=

⇓⇓ statistically significant reduction
* obtained at the 2nd month of treatment
** obtained at the 4th month of treatment

cerebrovascular diseases, the positive results obtained in this study are worth of note. Large prospective clinical trials based on these phathophysiological considerations are therefore highly recommended.

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