Eur Arch Psychiatry Clin Neurosci (2001) 251 : 247–254

ORIGINAL PAPER

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Naftidrofuryl in the treatment of vascular dementia

Received: 13 February 2001 / Accepted: 25 September 2001

Abstract The design of this study was based on the European guidelines for the treatment of Alzheimer's disease. After a placebo run-in period of 4 weeks, patients with a diagnosis of vascular dementia (VaD) were randomised to receive either 400 mg naftidrofuryl/day, 600 mg naftidrofuryl/day or placebo for 6 months. The patients were assessed using the ADAS-cog, the SCAG, the NOSGER and the CGI item 2 scale. The primary analysis was undertaken on the ITT population. At the end of the study, significantly more patients in the treatment groups showed no deterioration on both ADAS-cog and SCAG scales compared with placebo (400 mg p=0.005, 600 mg p=0.015). There were also significant differences between the active and placebo groups for the individual scales. This study has demonstrated that treatment with naftidrofuryl can slow the rate of deterioration of patients with vascular dementia.

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Key words cerebrovascular disease · dementia, vascular · naftidrofuryl · randomised controlled trials

Introduction

The past decade has seen a renewed interest in vascular dementia (VaD). After Alzheimer's disease (AD) it is the second most common dementia, affecting between 1.2 % and 4.2 % of the population aged more than 65 years, and up to 16.3 % of males aged over 80 years (Herbert R et al. 1995). Although the AD/VaD ratio is markedly affected by geographical variations, it is usually found to be > 1, being 1.36 in Finland and 3.25 in England (Herbert R et al. 1995). In only a few studies, particularly in Japanese populations, have figures shown a higher proportion of patients with VaD. Hence the relative prevalence of VaD, calculated as a percentage of all types of dementia and based upon post-mortem examination, ranges from 10 % in the UK (Wade JPH et al. 1987) to 48 % in Japan (Veda K et al. 1992). Whether the AD/VaD ratio is dependent on age does not seem to be completely clear; some studies reported that the ratio increased in higher age groups, whereas others have noted consistent AD/VaD ratios. Despite some variation, both genders seem to be similarly affected by VaD (male/female ratio 0.75 to 1.38).

Although the pathogenesis of VaD is far from fully understood, the main causes are believed to be multiple infarcts, white matter ischaemia or a strategically placed infarct leading to cerebral ischaemia and loss of brain tissue. However the differential diagnosis of VaD from AD remains a contentious issue. Hachinski was the first to develop a specific scale (Hachinski et al. 1975). However during the last decade the discriminatory power of the Hachinski scale (HIS) has been challenged. A joint working group of the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN) recently proposed new criteria for the diagnosis and differential diagnosis of the dis-

ease (Roman MD et al. 1993) as did the State of California Alzheimer's Disease Diagnostics and Treatment Centres (ADDTC) (Chui HC et al. 1992). Additional criteria to those included in the HIS are the presence of focal signs such as hemiparesis, facial weakness and Babinski sign and evidence of vascular lesions as identified by brain imaging. The relationship between the symptoms of dementia and the evidence for cerebrovascular disease should also be established.

The increased understanding of the pathogenesis of both AD and VaD has led to the development by the European Agency for the Evaluation of Medicinal Products of guidelines for the evaluation of anti-dementia drugs in which there are recommendations for the a priori selection of only those patients with AD (European Agency for the Evaluation of Medicinal Products 1997). In addition the International Working Group on Harmonisation of Dementia Drug Guidelines (IWG) made recommendations for two alternative study designs to evaluate drug treatment of dementia (Bodick N et al. 1997). To date there are no specific guidelines for the evaluation of drugs for the treatment of VaD although the European Agency do indicate that these general recommendations for AD can be adapted to other forms of dementia such as VaD. It is generally agreed that the main aim of treatment of VaD should be to prevent, or slow down, the progression of the atherosclerotic lesions. However because the disease manifests itself once the vascular lesions have already developed, a secondary therapeutic aim is to slow down, or arrest, symptom development. With this in mind the European guidelines recommend that the evaluation of any treatment for dementia should include assessment at three levels: cognitive, overall clinical response and activities of daily living.

Naftidrofuryl is a serotonin 5HT2 receptor antagonist which has been shown to inhibit serotonin-induced vascular smooth muscle contraction (Oudart N 1990) and platelet aggregation (Kirsten et al. 1995). In addition, under ischaemic conditions, it restricts aerobic metabolism resulting in increased ATP concentrations and a reduction in the lactate pyruvate ratio (Takeo S et al. 1991). Experimentally, it has been shown to induce an improvement in T maze test performance in rats following an experimental ischaemic event, suggesting a protective effect of the drug on the cognitive consequences of cerebral ischaemia (Lamproglou Y et al. 1992). In view of the important role that ischaemia plays in vascular dementia, naftidrofuryl would therefore seem to have a pharmacological profile which justifies investigation in the treatment of this condition.

Clinically it has been evaluated in placebo-controlled studies involving a total of more than 1100 patients, which included patients with senile dementia or cerebral impairment using doses ranging between 300 mg and 600 mg naftidrofuryl daily (Moller HJ 1997).

The results of the four most recent of these studies are summarised in Table 1 (Bornstein S et al. 1993, Grossman WM et al. 1990, Israel L et al. 1989, Saldmann et al. 1991).

Table 1 Summary of results of some major double-blind placebo-controlled studies of naftidrofuryl in patients with senile dementia

Reference	Dosage (duration)	No of patients	Assessment criteria	Relative efficacy (naftidrofuryl vs placebo)
Bornstein et al. [13]	600 mg/day (3 months)	87	Psychometric tests	$P < 0.01$
			SCAG	$P < 0.01$
Grossman et al. [14]	600 mg/day (8 weeks)	51	Psychometric tests	$P < 0.025$
			EEG	$P < 0.01$
Israel et al. [15]	600 mg/day (4 months)	56	Psychometric tests	$P < 0.05$
			Behavioural rating scales	$P < 0.01$
Saldmann et al. [16]	400 mg/day (3 months)	78	Psychometric tests	$P < 0.001$
			Behavioural rating scale	$P < 0.05$

EEG electroencephalogram; *SCAG* Sandoz Clinical Assessment Geriatric Scale

However the studies were of relatively short duration, and only in the study by Grossman was an attempt made to separate the patients into those with AD from those with VaD and a mixed pathology using the HIS. Only 12 patients with VaD and 15 with a mixed pathology were recruited, and whilst there was some evidence of an improvement in the naftidrofuryl group, the numbers were obviously too small to draw any conclusions about the value of naftidrofuryl in the treatment of VaD.

We therefore decided to undertake a study to specifically investigate the effects of naftidrofuryl in the treatment of vascular dementia.

Experimental procedures

Study plan and design

The aim of the study was to examine the efficacy and safety of oral naftidrofuryl in the treatment of vascular and 'mixed type' dementia. The study was designed as a 6 month prospective, controlled, randomised, double blind, multicentre study with a parallel group comparison between naftidrofuryl 400 mg/day, naftidrofuryl 600 mg/day and placebo.

Patients between 50 and 85 years of age who fulfilled the criteria for vascular or mixed type dementia, according to the recommendations of the NINDs-AIREN workshop of 1993, were enrolled in this study (Roman MD et al. 1992). They had to have a minimum score on the cognitive subscale of the Alzheimer's Disease Assessment Scale (Mohs RC & Cohen L 1988; Rosen WG et al. 1985) (ADAS-Cog) of 18, a score of at least 35 on the Sandoz Clinical Assessment Geriatric Scale (SCAG) (Schader RI et al. 1974), a Hachinski Ischaemic Score (HIS) greater than 4 and a Mini Mental State Examination (MMSE) (Folstein MF et al. 1975) score between 16 and 23. The severity of dementia was classified accord-

ing to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM III-R) as mild, moderate or severe.

Computerised tomography (CT) or magnetic resonance imaging (MRI) evidence of cerbrovascular lesions was also a requirement for entry into the study.

The principal exclusion criteria were 1) dementia of any other type, 2) the presence of intracranial space occupying processes, 3) evidence of depression (a score on the Montgomery and Asberg Depression Rating Scale (MADRS) (Montgomery SA & Asberg M 1979) of > 22, 4) a history of epilepsy or of drug abuse, 5) the presence of any other serious illness which might compromise the patients' completion of the study or 6) treatment with non-permitted medication (pentoxifylline, buflomedil, nootropics, anti-depressants, psychostimulants, hypnotics, sedatives and neuroleptics). Treatment with low doses of short action benzodiazepines and neuroleptics was permitted as was therapy with acetylsalicylic acid, dipyridamole and ticlopidine.

On recruitment to this study each patient entered a 4 week run-in phase, during which they received placebo treatment only. They were then randomised by means of a computer-generated randomisation list to receive either placebo, 400 mg naftidrofuryl or 600 mg naftidrofuryl daily for 6 months. The trial medication consisted of white, unscored, plain biconvex tablets containing either 200 mg naftidrofuryl oxalate (Dusodril®) or a corresponding quantity of filling agent (placebo) to ensure that the tablets were identical in weight and appearance. The study was undertaken in accordance with the Declaration of Helsinki (World Medical Association 1996) and with Good Clinical Practice guidelines (Note for Guidance and Good Clinical Practice 1996).

Assessments

At baseline, a detailed medical history was undertaken including a precise history of all drugs taken and the patients underwent a complete clinical examination. A cranial CT scan or MRI was undertaken if no scan had been taken in the previous 6 months or if there were grounds for suspecting that the findings could have changed since the last scan. If standard haematological and biochemical screening had not been undertaken within the previous two weeks, blood and urine samples were taken for measurement of these values. This screening was repeated at the end of the study. A drug screening for substances of abuse and other specified neuroleptic drugs was performed using the Trage 8 test kit (Merck KGaA, Darmstadt).

At baseline, and at randomisation, the HIS, MMSE and the MADRS scales were completed; the MADRS scale was also repeated at the end of the study. Of the two primary outcome variable measures, the SCAG was completed at baseline (Visit 1), randomisation (Visit 2) and then at 6 (Visit 3), 12 (Visit 4), 18 (Visit 5) and 26 (Visit 6) weeks and the ADAS-cog at Visits 2, 4, 5 and 6. The Nurses Observation Scale for Geriatric Patients (NOSGER) was completed at each of Visits 2 to 6 and the Clinical Global Impression (CGI) (National Institute of Mental Health 1976) item 2, which measures change, at Visits 3 to 6. Completion of the ADAS-cog was carried out by clinical psychologists, the results being kept blind from the investigator. The NOSGER scale was completed by a person to whom the patient was related and with whom they had daily contact. All other scales were completed by the investigating physician. Prior to the start of the study both the psychologist and the physician were required to undergo training of how to complete the respective test scales.

At each visit the patients and their relatives or carers were questioned on the occurrence of any unwanted events.

Statistical analysis

The characteristics of the patient groups were analysed at the beginning of the study using the Chi-square or Student t test for independent samples. The primary evaluation of efficacy was undertaken by recording the change in score in two validated dementia scales, the ADAS-cog and the SCAG scale. The outcome for each patient was defined as a therapeutic success if there was no deterioration recorded on either of these two scales, i. e. if final ADAS-cog ≤ baseline and final SCAG ≤ baseline. In order to detect a difference between the treatment groups with at least 20 % in this response rate, it was calculated that 125 patients per group were required (alpha error 0.05, beta error 0.1).

The primary analysis was undertaken on the intention to treat (ITT) population, defined as those patients who were randomised and provided key data on at least one occasion after baseline, using the last observation carried forward (LOCF) procedure. An additional analysis on the per protocol (PP) population was undertaken. The difference in response rates between the three groups was compared by a sample Chi-square test of difference of proportions and a Mantel-Haenszel test with adjustment for initial severity. Multiple comparisons between the treatment groups were undertaken, placebo vs 400 mg/day, placebo vs 600 mg/day and 400 mg/day vs 600 mg/day. The statistical analysis was undertaken prior to code break.

Results

Forty centres participated in the study; 403 patients were screened and 378 randomised following the 4 week placebo run-in period. Twenty of these patients were subsequently found not to have satisfied the initial inclusion criteria and a further 19 did not provide any key data after baseline, leaving 339 patients who constituted the ITT sample. Shown in Table 2 are the demographic characteristics of these patients: 118 in the placebo

Table 2 Baseline characteristics of ITT population expressed as means ± standard deviation or percentages

	Placebo N=118	400 mg N=113	600 mg N=108	P
Age (yrs)	72.5±8.0	70.6±8.2	71.5±7.7	NS
Sex				
Male	44.1%	41.6%	50.9%	NS
Female	55.9%	58.4%	49.1%	
DSM III-R dementia				
Mild	39.8%	42.5%	46.3%	
Moderate	56.8%	53.1%	48.2%	NS
Severe	3.4%	4.4%	5.6%	
SCAG	51.0±8.3	52.3±9.8	50.7±8.6	NS
ADAS-cog	28.6±7.7	29.0±8.5	29.5±7.5	NS
NOSGER	69.6±15.4	69.8±14.3	66.2±15.8	NS
MMSE	19.7±1.8	19.5±1.9	19.7±1.8	NS
Hachinski	8.5±2.5	8.7±2.5	8.8±2.3	NS
MADRS	14.3±3.8	14.0±3.4	14.0±3.7	NS

group and 113 and 108 in the 400 mg and 600 mg groups respectively, and their initial scores on the ADAS-cog, SCAG, NOSGER, MMSE and Hachinski scales.

There were no significant differences between the three groups for any of these values.

There were also no significant differences between the three groups for smoking behaviour, alcohol consumption, concomitant disease and previous or current medication.

The PP population comprised 90 patients in the placebo group, 95 in the 400 mg group and 93 in the 600 mg group. As with the ITT population there were no significant differences between the groups with regard to any of the baseline variables.

Efficacy data

The results for the primary and secondary variables as well as the number of patients in each group with no deterioration on ADAS-cog + SCAG, ADAS-cog, SCAG, NOSGER and CGI, defined as the response rate, are summarised in Table 3.

For the primary outcome measure, in which the outcome was defined as a success if final ADAS-cog ≤ baseline and final SCAG ≤ baseline, there were significant differences in the response rate in relation to the treatment for 400 mg/day vs placebo and for 600 mg/day vs placebo but not between 400 mg/day and 600 mg/day. Overall there was a significant difference in the response rate in relation to treatment (p=0.007). Similar differences were seen in the PP population.

The percentage of patients who deteriorated was thus reduced from 42% in the placebo group to 25% and 27% respectively in the 400 mg and 600 mg group. As the response rates in the 400 mg and 600 mg dose groups were similar their scores were pooled. Compared to the placebo group the relative risk of deterioration for the pooled treated group was 0.61 [CI 0.45, 0.83], equivalent to a 39% reduction.

The response rate on the combined SCAG and ADAS-cog scales were also calculated after adjustment for the initial severity of the dementia according to the DSM III-R category. Patients were divided into two groups, mild and moderate/severe. The results in the three treatment groups are shown in Fig. 1.

The overall response rate was higher in the mild group. A significant difference in the response rate adjusted for the initial severity of dementia was seen for 400 mg/day vs placebo, for 600 mg/day vs placebo but not for 400 mg/day vs 600 mg/day.

For the ADAS-cog scale alone, in which treatment was considered successful if the final scores were equal or lower than those at baseline, there were significant differences between 400 mg/day and placebo, between 600 mg/day and placebo but not between 400 mg/day and 600 mg/day (see Table 3).

The percentage of patients who deteriorated was thus reduced from 33% in the placebo group to 16% and 18% in the 400 mg and 600 mg groups respectively.

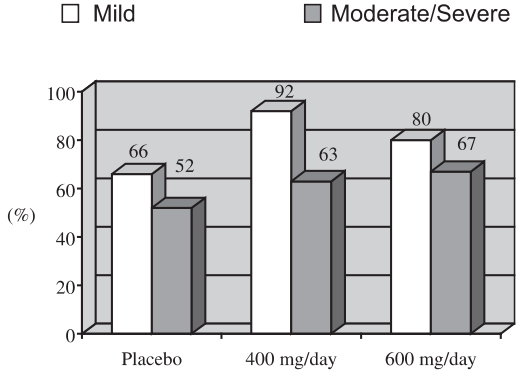

Fig. 1 Response rate (no deterioration on ADAS-cog and SCAG) according to initial disease severity in the ITT population (400 mg vs placebo p=0.005, 600 mg vs placebo p=0.020, 400 mg vs 600 mg p=0.62).

Table 3 Overall response rate (no deterioration) for ADAS-cog + SCAG, ADAS-cog, SCAG, NOSGER and CGI in ITT population

	Response rate (%)			Pairwise comparison p value		
	Placebo	Naft 400 mg	Naft 600 mg	Placebo vs 400 mg	Placebo vs 600 mg	400 mg vs 600 mg
ADAS-cog + SCAG	58	75	73	0.005	0.015	0.73
ADAS-cog	67	84	82	0.003	0.013	0.61
SCAG	65	84	84	0.001	0.001	0.97
NOSGER	50	63	58	0.049	0.21	0.49
CGI	55	73	66	0.004	0.10	0.21

Compared to placebo the relative risk of deterioration for the pooled treated group was 0.52 [CI 0.35, 0.77], i. e. the observed risk of deterioration in the treated groups was about half of that in the placebo group.

The response rates on the ADAS-cog according to the initial severity of the disease are shown in Fig. 2.

The response rates were significantly lower in the placebo patients than for those treated with 400 mg/day or 600 mg/day but there was no difference between the two active treatment groups.

For the SCAG scale alone, in which treatment was considered successful if the final scores were equal to or lower than those at baseline, there were significant differences between both naftidrofuryl groups and the placebo group but not between the two active treatment groups (Table 3).

The percentage of patients who deteriorated was thus reduced from 35 % in the placebo group to 10 % in the two active groups. Compared to the placebo group, the relative risk of deterioration for the pooled group was 0.46 [CI 0.31, 0.67], i. e. the observed rate of deterioration in the treated groups was less than half of that in the placebo group.

The response rates on the SCAG according to the severity of the disease are shown in Fig. 3.

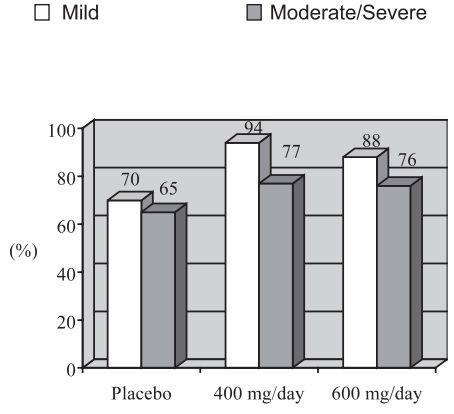

Fig. 2 Response rates on the ADAS-cog scale according to initial disease severity (ITT population) (400 mg vs placebo p=0.003, 600 mg vs placebo p=0.017, 400 mg vs 600 mg p=0.53).

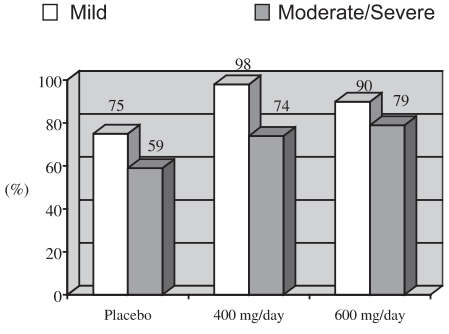

Fig. 3 Response rates on SCAG according to initial dementia severity (ITT population) (400 mg vs placebo p=0.001, 600 mg vs placebo p=0.002, 400 mg vs 600 mg p=0.92).

The response rates, adjusted for initial disease severity, were significantly lower in the placebo group than for those treated with 400 mg/day or 600 mg/day but there was no difference between the two active treatment groups.

For all these analyses similar response rates were observed in the PP population and, as in the ITT population, there were significant differences between the two active dosage groups and placebo, but not between the two active dosage groups.

For the NOSGER scale, in which a final score less or equal to the baseline values was defined as success, a significant difference in the response rates was seen between 400 mg/day and placebo but not between 600 mg/day and placebo or between 400 mg/day and 600 mg/day (Table 3).

The NOSGER response rates, adjusted according to initial disease severity, are shown in Fig. 4. In contrast with all the other assessment scales, a better response on active treatment was seen in the moderate/severe group than in the mild group. However overall there was no significant difference between any of the treatment groups.

Finally for the CGI item 2 score, in which success was defined as any improvement in score, there was a significant difference between the overall response rate in the 400 mg/day vs the placebo group but not between 600 mg/day and placebo or between 400 mg/day and 600 mg/day (Table 3).

The response rates adjusted for initial disease severity are shown in Fig. 5. There were significant differences in the response rates in the CGI item 2, adjusted for initial disease severity, between the 400 mg/day and placebo but not between 600 mg/day and placebo or 400 mg/day and 600 mg/day.

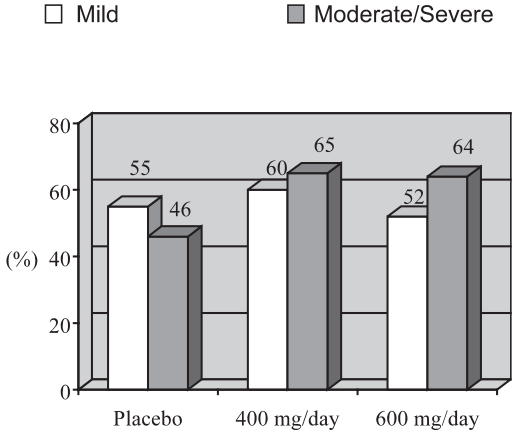

Fig. 4 Response rates on NOSGER scale according to initial disease severity (ITT population) (400 mg vs placebo p=0.052, 600 mg vs placebo p=0.21, 400 mg vs 600 mg p=0.52).

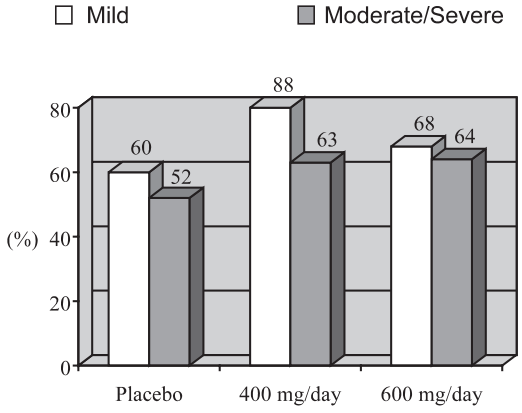

Fig. 5 Response rates on CGI item 2 score according to initial disease severity (ITT population) (400 mg vs placebo p=0.004, 600 mg vs placebo p=0.12, 400 mg vs 600 mg p=0.18).

Treatment compliance

Of the ITT population 94 % was shown, by individual tablet count, to achieve a treatment compliance level of at least 80 % of the prescribed medication.

Mortality and safety data

A total of 47 serious adverse events were reported by 45 patients after randomisation: 20 in the placebo group and 12 and 15 in the 400 mg and 600 mg groups respectively. None of the reported symptoms were considered by the investigators as being either possibly or probably related to the study medication. Four patients died during the study period, one due to myocardial infarction or circulatory failure (400 mg group), one due to cardiac failure (600 mg group), one due to sudden cardiac death (600 mg group) and one due to multi-organ failure (placebo group).

There were no clinically relevant changes in laboratory and haematological values during the course of the study.

Discussion

Currently there is no definitive medical or surgical treatment for vascular dementia (Nyenhans DL, Gorelide PB 1998). Treatment of the risk factors for stroke, in particular hypertension, may offer the best opportunity, in the longer term, of lowering the incidence rates for this condition. However currently such evidence is limited and whilst one recent study claimed to demonstrate such an outcome (Forette F et al. 1998), other authors have suggested that the conclusions of this study should be treated with caution (Pahor M et al. 1999, Zuccala G et al. 1999). Once VaD occurs, control of risk factors for stroke may be useful, although some authors have found that elevation of blood pressure may be protective for such patients (Gerelick PS et al. 1993).

One of the main difficulties in evaluating the effects of drug treatment in vascular dementia is the lack of internationally validated disease specific instruments. Most of those now available were originally developed and validated for AD patients. The European Guidelines state that any assessment of a potential treatment for dementia should include evaluation of cognitive function, ideally by a clinical psychologist, assessment of daily living activities by a relative or carer, and a global clinical assessment of the patient by a physician. However, having selected what we believe were the most suitable scales to cover these areas, the ADAS-cog, the NOSGER and the CGI and SCAG we were then left with the problem as to how they should be analysed to ensure that any change in the status of the patient recorded over the duration of the study was clinically relevant. We decided to do this, as recommended in the current European guidelines, by calculation of the response rate, which involved, for each scale, comparison of the final score with the initial score, and then calculation of the percentage of patients in each group whose score remained the same or improved. The use of response rates to evaluate the clinical relevance of drug effects in the treatment of dementia has been criticised (Whitehouse PJ et al. 1998); however we believe that it does provide a simple means of determining whether the treatment slowed down, or arrested, symptom development. Such an endpoint provides a simple answer to the question, did the treatment prevent deterioration in the patient's condition that is, did it slow down, or arrest, symptom development.

Using the two primary measures of efficacy used in this study, the SCAG and ADAS-cog, we have shown a significant improvement in the response rate, defined as the proportion of patients who did not deteriorate, following treatment with naftidrofuryl. This improvement was seen with both the 400 mg and 600 mg dose groups. Thus for the SCAG the relative risk of deterioration in the pooled sample compared with placebo was more than halved (–54 %), with similar reductions also being demonstrated on ADAS-cog (–48 %). In taking into account both the physicians and psychologists assessment, that is, calculating the proportion of patients whose final SCAG and ADAS-cog scores were equal to, or better than, the baseline values, treatment with naftidrofuryl was shown to produce a 39 % reduction in the overall risk of the patient deteriorating, a figure which we believe represents a clinically worthwhile outcome. These treatment effects were seen in both mild and moderate/severe DSM III-R category patients.

Although there was evidence of an improvement in ADL, as measured by the NOSGER at the 400 mg dose, it was interesting to note that the effect was greater in the more severely affected patients. It may be that the relatives or carers who completed this scale found it more difficult to evaluate changes in mild patients than in those with more severe symptoms.

In conclusion, by calculation of a response rate based upon the ADAS-cog and SCAG scales we have demonstrated that naftidrofuryl, when given at both 400 mg

and 600 mg daily, slowed down the rate of deterioration of patients with vascular or mixed type dementia over the 6 month treatment period. These treatment effects were seen in both mild and moderate/severe DSM IIIR category patients. The higher dose did not provide any additional benefit. These results confirm the finding of a recently published study in which patients with vascular or mixed dementia were treated with naftidrofuryl for 12 months and which also demonstrated statistically significant improvements in cognitive and global function in this patient population (Emeriau J-P et al. 2000).

Appendix

List of investigators and study centres

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