New approach to treatment of recent stroke

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Summary and conclusions

Ninety-one patients with acute stroke participated in a double-blind, placebo-controlled trial of naftidrofuryl. Treatment was allocated at random and given over 12 weeks, neurological and neurophysical scores being obtained before treatment and at weeks 2, 4, 8, and 12.

Both treatment groups greatly improved over the 12 weeks, but the naftidrofuryl-treated patients made greater neurological progress. Of the patients eventually discharged, those given naftidrofuryl spent only half as long in hospital as the controls. Deaths attributable to stroke were significantly fewer in the active-treatment group.

Introduction

In the UK some 55 000 new cases of stroke occur yearly. Furthermore, the NHS has to provide 18 000 beds a day for 100 000 hemiplegic patients severely handicapped by cerebral vascular disease. Thus a treatment is needed to reduce the morbidity in these patients, or even the mortality rate, which is 40-50% within the first three weeks. Conventional drug treatment is aimed at reducing cerebral oedema or increasing blood flow to areas of the brain rendered ischaemic but not irretrievably damaged. Another possible approach is the use of naftidrofuryl, which has a direct effect on intracellular metabolism[1] and protects cells against the results of ischaemia.[2 3]

I report the results of a double-blind controlled trial of naftidrofuryl in patients with acute stroke admitted to the Sheffield Stroke Rehabilitation Unit at the Northern General Hospital.

Patients and methods

Ninety-one patients entered the study, which was conducted over 16 months from June 1976. All were considered to have had a stroke due to recent ischaemic cerebral infarction and satisfied the following criteria: they had not previously suffered a stroke; they were conscious; they had no previous history of dementia; they had no history of severe confusion; their stroke was due to vascular causes only. Forty-six of the patients were women and 45 men, and their average age was 73·3 years (range 56-89).

As soon as possible after admission to the unit all patients had been examined by a clinician and a team of therapists. Once found suitable for the study they were allocated at random by means of a numerical code to 12 weeks' treatment with either naftidrofuryl or placebo. Neither the staff nor the patients knew to which group they had been allocated. Patients in the active-treatment group received two 100 mg capsules of naftidrofuryl three times daily for four weeks, then one capsule three times daily for eight weeks. Controls received an identical regimen of placebo capsules containing lactose. Side effects, associated disease, other treatment, and cause of death (where applicable) were recorded.

On entry to the study all patients underwent full neurological and neurophysical assessment based on eight main variables subdivided as shown in table I. Patients were rated 1 to 4 (1 poor, 2 fair, 3 good, 4 normal) for each subdivision and the totals summed to give an overall score. Assessments were repeated at 2, 4, 8, and 12 weeks; in those patients who were discharged before the trial was completed the rest of their assessments were undertaken at home.

TABLE I—*Neurological and neurophysical variables assessed on entry to study*

- Power:
  - Arm
  - Leg
- Sensations:
  - Pain
  - Touch
  - Temperature
  - Vibration sense
  - Sense of position
- Cerebellar functions:
  - Ataxia
  - Nystagmus
  - Incoordination
- Speech:
  - Motor (speaking, writing)
  - Sensory (auditory, visual)
  - Mixed
- Sphincter controls:
  - Bladder
  - Bowel
- Mental functions:
  - Concentration
  - Orientation of time and place
  - Recent memory
  - Recall memory
  - Past memory
  - Hallucinations
  - Delusions
- Activity of daily living:
  - Toilet
  - Bathing
  - Dressing
  - Feeding
  - Washing
  - Shaving/hairdressing
  - Cooking
- General functions:
  - Balance
  - Walking
  - Sitting
  - Turning
  - Standing
  - Climbing stairs

Results

Of the 91 patients, 47 were allocated to the active-treatment groups and 44 to the control group. There was no appreciable difference between the groups in sex distribution, age, interval between stroke and inclusion in the study, or initial overall assessment score (table II). Thus the two groups were fully comparable.

TABLE II—*Pretreatment details of the active-treatment and control groups*

	Active-treatment group	Control group	Significance of difference
No of patients	47	44	
Men	25	20	NS ($\chi^2 = 2{\cdot}17$)
Women	22	24	
Mean age ± SD (years)	73·45 ± 7·32	73·16 ± 6·49	NS ($t = 0{\cdot}20$)
Mean (± SD) interval from stroke to treatment (days)	5·04 ± 5·30	5·88 ± 6·10	NS ($t = 0{\cdot}70$)
Mean initial overall assessment score	90·34	93·02	NS (Mann-Whitney U test = 0·05)

NS = Not significant.

At the completion of the study the overall assessment scores had increased considerably in both groups. Owing to non-continuity of the data, however, it was not considered appropriate to analyse these by the usual parametric tests, so the non-parametric Mann-Whitney U test was used. The mean initial overall score in the active-treatment group (93·06) was slightly lower than in the control group (96·65), but not significantly so (see table III). At the end of the study the mean overall score in the active-treatment group (124·20) was significantly higher than that in the control group (114·37) ($P < 0{\cdot}05$).

Table III lists the mean scores for the eight main variables studied. For all variables except power the active-treatment group had slightly lower mean scores initially; nevertheless, the final scores in the active-treatment group were greater in all cases. The variables were clearly interrelated, and no single variable stood out as the main cause for the overall improvement.

By the end of the 12 weeks 24 controls and 23 patients in the active.

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TABLE III—*Mean initial and final assessment scores in the two groups*

	Initial scores		Final scores	
	Active-treatment (n = 38)	Control group (n = 31)	Active-treatment (n = 38)	Control group (n = 31)
Power	3·79	3·65	5·79	4·61
Sensations	9·63	9·84	15·47	13·19
Cerebellar functions	8·95	9·55	10·89	10·16
Speech	14·53	16·03	17·18	16·71
Sphincter controls	5·08	5·35	6·76	6·42
Mental functions	18·55	19·03	23·53	22·06
Activity of daily living	16·82	17·26	23·42	21·61
General functions	15·71	15·94	21·16	19·61
Overall	93·06*	96·65*	124·20†	114·37†

*NS (Mann-Whitney U test = 0·64).
†P < 0·05 (Mann-Whitney U test = 2·27).

treatment group had been discharged. Those given naftidrofuryl, however, had spent a significantly shorter time in hospital than the controls (mean 26·13 ± SD 19·54 days compared with 51·33 ± 21·05 days—$t = 4·24$; $P < 0·001$). Twenty-two patients died during the study, 13 in the control group and nine in the active-treatment group. This difference was not significant. Eleven deaths in the control group, however, compared with only four in the naftidrofuryl-treated group were attributable to stroke ($\chi^2 = 4·49$; DF = 1; $P < 0·05$).

Minor side effects were noted in five of the naftidrofuryl-treated patients and one of the controls. They did not necessitate withdrawal from treatment.

Discussion

Naftidrofuryl enhances cellular energy metabolism,[1-3] and several double-blind controlled trials have confirmed its value in senile dementia.[4-10] The relevance of these findings has been sharpened by the view that primary senile dementia is not due to atherosclerosis[11] and the observation that drugs acting on the cerebral circulation are of little value in elderly confused patients.[12] The term senile dementia, however, covers several possibly related or identical diseases—for example, chronic brain failure, senile organic brain failure, and cerebral vascular insufficiency. I set out to examine the effects of naftidrofuryl on a specific condition—namely, acute stroke.

Whatever the cause of stroke, the resultant ischaemia produces an area of neuronal damage surrounded by a further area of cells that may not be irretrievably damaged. Naftidrofuryl is claimed to protect cells against the metabolic effects of ischaemia,[13] so its use seems a logical approach to treatment. Measurement of the effects of naftidrofuryl on the cerebral metabolism is impracticable, however, hence the results must be assessed clinically.[14] Since no one scale of psychometric assessment is ideally suited to the evaluation of patients with stroke my colleagues and I have produced a simple scoring system that covers all variables likely to be important.

My results show that after 12 weeks' treatment with naftidrofuryl the extent of recovery was significantly greater than after identical administration of placebo. But probably the salient finding was that patients treated with naftidrofuryl were able to leave hospital on average 25 days sooner than those not given the drug. This is of considerable importance in view of the shortage of hospital beds in the UK.

Significantly fewer of the naftidrofuryl-treated patients died as a direct result of stroke. Nevertheless, the total death rate in the series was only 24% compared with the 40-50% quoted elsewhere. In part this was certainly due to the exclusion of unconscious patients. Investigation of this aspect of naftidrofuryl's therapeutic potential with more severely disabled patients seems worth while.

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ONE HUNDRED YEARS AGO The remarkable effects produced by metallotherapy in cases of hemianaesthesia originating from hysteria are well known to our readers. There have, however, of late been made new experiments by Dr Thermes with thermic-stimulants, which have produced the same effect as the metals on different hysterical complications, such as anaesthesia, achromatopsy, and contractions. The following is a brief summary of the results observed on hysterical hemianaesthestic patients. Cold and heat were successively applied—the well known first stages of thermic stimulation. A piece of ice was applied to the left temporal and supraorbital regions of a patient suffering from hemianaesthesia of the left side and from achromatopsy. After fifty or sixty seconds had elapsed, the left eye began to be able to distinguish colours—first blue, then red, yellow, and purple; but the right eye was at the same time affected by amblyopia. The parts that had come into contact with the ice recovered their natural sensibility; but the corresponding parts on the right side became anaesthetic. The piece of ice was then brought into contact with the left forearm, which was, as before mentioned, insensible. Two minutes later, not only the place touched by the ice, but also the entire arm up to the shoulder, was perfectly normal. At the same time, the muscular strength of the arm suddenly increased from 11, as had been previously tested by the dynamometer, to 23; but the right upper extremity became weak and insensible. Two or three minutes after the removal of the ice, these phenomena had disappeared and everything returned to its normal state. Iced water produced the same effects, only more slowly. A general douche of cold water gave the same results as the ice, only in a more general way, all the troubles disappearing in the left side and being transferred to the right side, which had been the healthy one. Contraction was either entirely removed by the douche or transferred. The results were much more remarkable if the water were very cold and it were projected with considerable force. The anaesthetic hand recovered its sensibility after having been plunged into water of 40 deg C (104 deg Fahr) for thirty or sixty seconds; and the same effect was produced gradually on the whole arm up to the shoulder, while the corresponding right side was affected as before. This effect lasted only two minutes after the hand had been taken out of the water; but, if the immersion continued, the hand became insensible as before. A sponge imbibed with water of 49 deg Cent and applied to the face gave exactly the same result as the piece of ice did. If the temperature of the water were near 50 deg C, the effects were much more marked. Contraction did not resist heat, and often disappeared for several hours altogether. A douche of hot water (33 to 40 deg C = 91·4 to 104 deg Fahr) called forth the same phenomena as did the cold water: the hysterical symptoms left the side that had been previously affected and attacked the side that had been well. If the douche were continued, anaesthesia took place again in its previous places. (*British Medical Journal*, 1878.)