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A Double-Blind Placebo-Controlled Study of the Effects of Amphetamine and Physiotherapy after Stroke

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Amphetamine · Stroke · Rehabilitation

Abstract
Major therapeutic advances in the rehabilitation of subacute stroke are lacking. One promising approach is treatment with amphetamine in combination with physiotherapy so as to promote motor function. In a randomized, double-blind, placebo-controlled clinical trial, the effect of 10 sessions with 10 mg of amphetamine combined with physiotherapy during a 5-week period was investigated in 39 geriatric patients who had been admitted to a stroke rehabilitation unit. Motor function (Fugl-Meyer motor performance score) and activities of daily living (ADL; Barthel's index) were assessed at baseline and at the end of treatment. All patients improved significantly over the intervention period. Amphetamine-treated patients did not show any increase in motor function or ADL as compared to the control group. Rehabilitation with amphetamine at this dosage and interval, combined with physiotherapy, did not promote motor recovery or functional capacity in patients suffering from stroke.

Introduction

Studies by Feeney [1] have shown that modulation of brain catecholamines with amphetamine may influence recovery after stroke, but only when given together with 'symptom-relevant experience', that is, concomitant training sessions. Positive results from several animal studies in the form of increased motor function after stroke [2–4] were followed by small-scale human studies where amphetamine in combination with physiotherapy has been reported to further improve motor recovery. Crisostomo et al. [5] showed that four stroke patients treated with a single dose of 10 mg of amphetamine 3–10 days after stroke paired with physiotherapy had significantly greater improvement in motor function as compared to a placebo group. In another randomized controlled study by Walker-Batson et al. [6], 10 hemiplegic stroke patients with severe motor deficits received either 10 mg of dextroamphetamine or placebo orally every 4th day for 10 sessions paired with physiotherapy. The first session started 16–30 days after stroke. The motor performance in the therapy group had increased significantly as compared to the placebo group 1 week after the treatment sessions were finished [6]. Two other reports, including 20 and 25 patients, respectively, were not able to reproduce these findings [7, 8].

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It is difficult to conclude which is the most effective study since there is a great variation in the type of design, such as the start of treatment and concomitant physiotherapy. Also, the power is low due to the low number of patients. Here, we conducted a randomized, double-blind, placebo-controlled clinical trial with a similar design to that used by Walker-Batson et al. [6]. The objective of our study was to investigate the effect of 10 sessions of an oral dose of amphetamine combined with physiotherapy, starting 5–10 days after stroke.

Patients and Methods

During the period from November 1998 to June 2000, 364 patients were admitted to the geriatric rehabilitation ward at Huddinge University Hospital because of an acute stroke. Patients were examined by the physician in charge (J.L.). The medical examination included a medical history, assessment of somatic and neurological status, laboratory analysis and CT scan.

Patient Selection

Geriatric patients (65 years or over) with a paretic arm and/or leg following a stroke which had occurred 5–10 days previously and who could follow instructions were included. The presence of hemiplegia was defined as an arm motor score of 0–50 and a leg motor score of 0–30 on the Fugl-Meyer (FM) motor scale at baseline screening. Patients were excluded if they had had an earlier cerebral lesion with a documented need for care and remaining paretic symptoms and/or a serious disease, such as psychiatric, neurological, cardiovascular, respiratory, musculoskeletal, gastrointestinal, hematological or oncological disease, as assessed by the responsible physician. Patients receiving α-adrenergic antagonists or agonists, neuroleptics, benzodiazepines or antidepressants were also excluded. Forty patients were included in the study after their informed consent had been obtained.

Drug Administration and Randomization

Study patients and all other people involved were blinded to the treatment type. Drug treatment was given in the form of identical white tablets of 2 × 5 mg of either *d,l*-amphetamine or placebo 60 min before the training session. The drugs were supplied by the pharmacological company Recip AB, Stockholm, Sweden. The amphetamine/placebo was randomly distributed in boxes labeled 1–40. Patients received the boxes in consecutive order. All side effects during the intervention period were registered.

Physiotherapy

The physiotherapy intervention was based on functional movements including balance training, transfer training and more specific motor function training of the paretic arm/leg. Because of the clinical setting, the training varied from each patient depending on the severity of their paresis. All patients underwent at least 30 min of physiotherapy 5 days a week in addition to the ward's regular training program. The first of 10 study sessions took place within 5–10 days from the onset of stroke. Patients received amphetamine or placebo twice a week. Tablets were given 1 h before the start of physiotherapy. Patients discharged from the rehabilitation unit within 5 weeks continued the combination treatment irrespective of where they were discharged to. Patients discharged home were treated twice a week by a physiotherapist (M.N.) from the rehabilitation unit. When further rehabilitation was needed in a community rehabilitation unit, the responsible physiotherapist was informed of the study both orally and in writing, and he/she then continued the combination treatment until the 10th session. Compliance with the treatment was recorded by the physiotherapist in a protocol which was collected after the treatment period.

The study was approved by the Ethical Committee of Huddinge University Hospital.

Table 1. Baseline data of amphetamine-treated patients and placebo-treated controls

	Amphetamine group (n = 20)	Placebo group (n = 19)	p
Mean age, years	80 (6.2)	75 (4.4)	0.01
Range	71–91	66–83	
Males/females	10/10	13/6	0.25
Infarct/hemorrhage	19/1	18/1	0.97
Right/left paresis	7/13	11/8	0.16
FM total motor score	33.6 (25.8)	40.9 (27.9)	0.40
FM arm motor score	17.2 (15.9)	22.7 (20.4)	0.35
FM leg motor score	16.4 (11.1)	18.2 (9.3)	0.58
Barthels ADL index	43.8 (21.3)	50.8 (23.0)	0.33

p values were estimated with ANOVA. The figures in parentheses represent standard deviations.

Assessments

Motor function and activities of daily living (ADL) were assessed by a physiotherapist (L.S.) at baseline, at the end of the 10th session and at follow-up, 3 months after stroke. Baseline motor scores were obtained 1 day before study initiation in all patients. The score at the end of the treatment was determined the day after the 10th session. The FM motor performance score was used to evaluate changes in motor function. On this scale, a score of 0 points means no motor function and a score of 100 points indicates normal motor function (divided into 66 points for normal arm motor function and 34 points for normal leg motor function). This test is often used in stroke research and its reliability and validity are both well documented [9, 10]. Autonomy in ADL was evaluated with Barthel's index [11, 12]. This scoring system involves a weighted scale, ranging from 0 to 100 in 5-point increments, that measures performance in terms of self-care (feeding, bathing, personal toilet, dressing, bowel and bladder care), as well as locomotion (for instance moving between bed, wheelchair and toilet, ambulation and stair climbing). A score of 100 does not imply normality but rather that the patient is functionally independent in most ADL.

Study Size and Power

The variance and effect size needed to calculate the number of patients were estimated from the study of Walker-Batson et al. [6]. This revealed that a sample of 32 patients was necessary to achieve an 80% chance (power = 0.80) of detecting a mean difference of 20

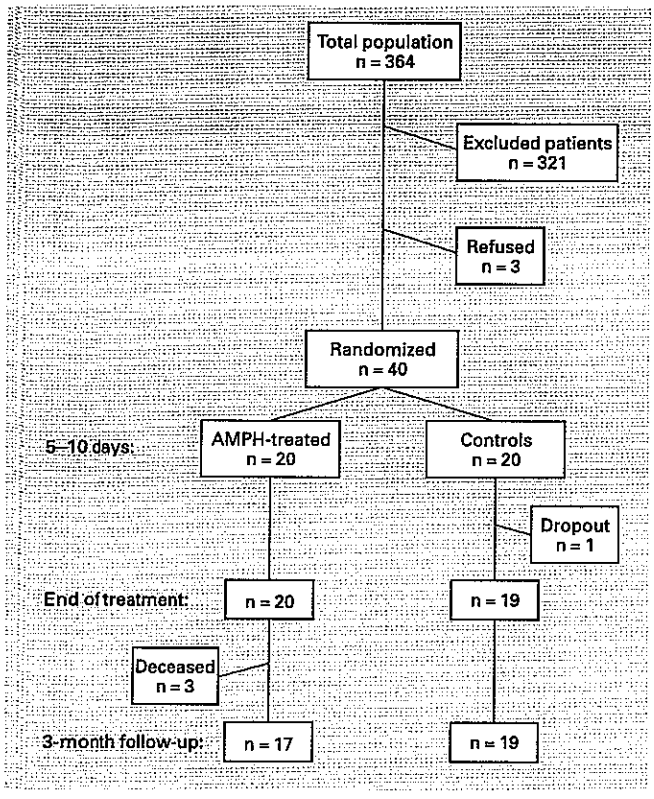

Fig. 1. Flow chart describing the subjects included and randomized in the amphetamine (AMPH) treatment study.

points in improvement between the two groups in the main outcome measure (FM score). This number was increased to 40 in anticipation of inevitable defaulters.

Statistics

The data are given as means ± SD. The Mann-Whitney U test was used to analyze the FM and Barthel data. Patients with total baseline FM scores below 36 (indicating severe motor deficits) were analyzed separately in order to compare results with those from the study of Walker-Batson et al. [6]. The effects of age and motor function on improvement during the study were tested with MANCOVA. All the analyses were done with SPSS statistic software.

Results

At baseline, the group treated with amphetamine did not differ significantly from the placebo group with regard to gender, side of paresis, motor function and ADL scores. However, the patients in the amphetamine group were significantly older than the controls (table 1).

Treatment with amphetamine or placebo was started on average 8 days after stroke onset in both groups. For 1

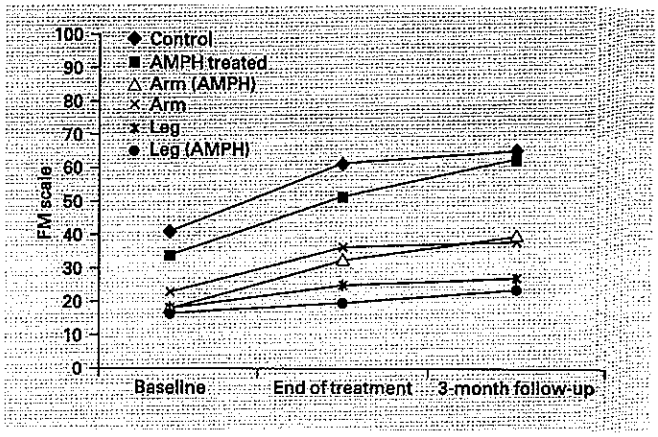

Fig. 2. Mean FM motor performance scale scores in patients treated with amphetamine (AMPH) and physiotherapy and controls. Total, arm and leg motor scores are shown.

patient in the control group, the treatment was discontinued after the second session because of acute renal insufficiency and uncontrolled hypertension. Data for this patient were not included in the analysis.Three patients in the amphetamine group died during the follow-up. They had severe motor deficits at baseline and the causes of death were a new cerebral infarction, bronchopneumonia and myocardial infarction, respectively (fig. 1).

Amphetamine-treated patients showed lower scores at baseline and at the end of treatment, but the difference was not significant. At follow-up, the remaining 17 patients in the amphetamine group had similar mean scores compared to controls (62.5 ± 27.8 vs. 65.2 ± 23.3). All patients improved significantly in motor function over the intervention period. However, the amphetamine group did not show a greater increase in motor function as compared to the control group, either at the end of treatment or at follow-up (fig. 2). Nor when a classical intention-to-treat analysis was used, including the last observation available for each subject, did the results change significantly (fig. 3).

The effects of age and baseline FM score were analyzed in a test of within-subject effects and these variables were used as covariates or as split variables (median split: 76 years for age and 26 points for total FM motor score). Neither age nor initial FM score showed significant interactions with treatment.

Patients with severe motor deficits (total baseline FM score below 36) were analyzed separately. Motor function did not show a greater increase in amphetamine-treated patients as compared to controls. Baseline mean FM

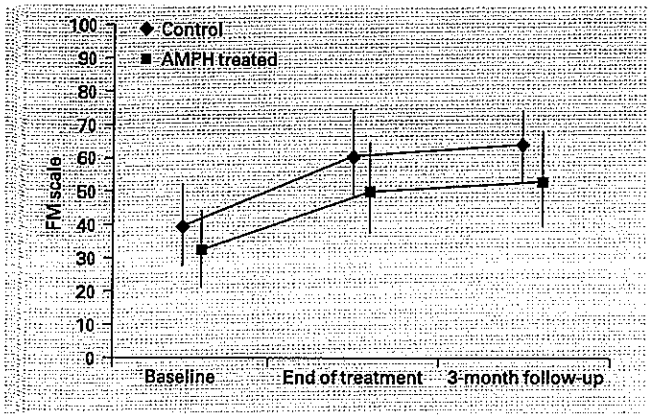

Fig. 3. Mean scores of the FM scale in patients randomized to amphetamine (AMPH) or the control group. Intention-to-treat analysis. Vertical lines denote the confidence interval.

scores were 18.2 ± 10.3 in the amphetamine group and 17.6 ± 8.1 in controls. Scores at the end of treatment were 40.9 ± 25.6 versus 41.8 ± 15.8 and at follow-up, 47.2 ± 28.9 versus 46.4 ± 15.3 in the amphetamine and control group, respectively.

ADL functions graded on Barthel's index improved over the intervention period, but the improvements were similar in the amphetamine group and controls. Amphetamine-treated patients showed lower scores at each evaluation time (Barthel scores at the end of treatment 62.8 ± 25.9 vs. 72.6 ± 23.4 and at the follow-up 69.1 ± 27.9 vs. 77.1 ± 20.8, respectively), but the difference was not significant.

Discussion

Our results showed that the treatment of stroke patients with amphetamine in combination with physiotherapy at a rehabilitation unit did not further improve motor recovery or functional outcome. A number of factors may have influenced the results. Our study was carried out in a geriatric stroke ward and the mean age of the treated patients was 80 years. This is a considerably higher age than that for the patients investigated in the two studies reporting increased recovery of motor function after amphetamine treatment [5, 6]. Our treatment group was also on average 5 years older than the controls and about 19 years older than the patients treated in the study of Walker-Batson et al. [6]. The amphetamine-treated patients in the study of Walker-Batson et al. [6] showed approximately similar motor scores as did the patients in the amphetamine group and the controls in our study at the end of treatment. It seems reasonable to think that age may influence the capacity for functional recovery. However, we do not think that this can explain our results. Buell and Coleman [13] showed that the loss of neurons in aging humans is to some extent compensated for by selective dendritic growth. Furthermore, the study by Ferrucci et al. [14] showed that the extent of improvement in functional status after a rehabilitation program was independent of age, although older patients may be more likely to employ compensatory strategies to overcome some of the neurological impairment that remained after stroke. The above-mentioned studies suggest a capacity for reorganization in aging humans.

Feeney [1] stressed the importance of administering amphetamine together with some kind of physical training or stimulation. We combined the daily standard training at the ward with amphetamine, which was administered 60 min before training twice a week for 5 weeks. The training schedule varied depending on the severity of each patient's condition after stroke. Exercises included training in weight bearing, balance, transfer and functional movement as well as facilitating the active use of the affected limb.

We do not know the optimal daily dose of amphetamine, the length of the treatment period or when we should start the treatment. The studies that are available have used different dosages and frequencies as well as intervention periods of different lengths. In our study and in the other studies, no serious adverse effects were seen during treatment (in line with the report of Unwin and Walker-Batson [15] using 10 mg of dextroamphetamine).

The number of patients in the present study and other studies was limited, which reflects the difficulties of enrolling patients in trials and which also affects the results. Although our present data are negative, amphetamine is the most extensively studied drug shown to promote recovery of function in animal models of stroke [16]. In order to find a possible and optimal regime of amphetamine to enhance motor recovery without adverse effects, future clinical studies should use a higher and/or more frequent dosage of amphetamine as well as a longer treatment period together with a greater number of patients.

Aknowledgements

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References

1 Feeney DM: From laboratory to clinic: Noradrenergic enhancement of physical therapy for stroke or trauma patients. Adv Neurol 1997; 73:383–394.

2 Feeney DM, Gonzales A, Law WA: Amphetamine restores locomotor function after motor cortex injury in the rat. Proc West Pharmacol Soc 1981;24:15–17.

3 Feeney DM, Hovda DA: Amphetamine and apomorphine restore tactile placing after motor cortex injury in the cat. Psychopharmacology (Berl) 1983;79:67–71.

4 Sutton RL, Hovda DA, Feeney DM: Amphetamine accelerates recovery of locomotor function following bilateral frontal cortex ablation in cats. Behav Neurosci 1989;103:837–841.

5 Crisostomo EA, Duncan PW, Propst M, Dawson DV, Davis JN: Evidence that amphetamine with physical therapy promotes recovery of motor function in stroke patients. Ann Neurol 1988;23:94–97.

6 Walker-Batson D, Smith P, Curtis S, Unwin H, Greenlee R: Amphetamine paired with physical therapy accelerates motor recovery after stroke. Further evidence. Stroke 1995;26: 2254–2259.

7 Mazagri R, Shuaib A, McPherson M, Deighton M: Amphetamine failed to improve motor function in acute stroke. Can J Neurol Sci 1995;22:25.

8 Reding M, Solomon B, Borucki S: Effect of dextroamphetamine on motor recovery after stroke. Neurology 1995;45:A222.

9 Duncan PW, Propst M, Nelson SG: Reliability of the Fugl-Meyer assessment of sensorimotor recovery following cerebrovascular accident. Phys Ther 1983;63:1606–1610.

10 Fugl-Meyer AR, Jaasko L, Leyman I, Olsson S, Steglind S: The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. Scand J Rehabil Med 1975;7:13–31.

11 Collin C, Wade DT, Davies S, Horne V: The Barthel ADL Index: A reliability study. Int Disabil Stud 1988;10:61–63.

12 Mahoney FI, Barthel DW: Functional evaluation: Barthel index. Md State Med J 1965;14: 61–65.

13 Buell SJ, Coleman PD: Quantitative evidence for selective dendritic growth in normal human aging but not in senile dementia. Brain Res 1981;214:23–41.

14 Ferrucci L, Bandinelli S, Guralnik JM, Lamponi M, Bertini C, Falchini M, Baroni A: Recovery of functional status after stroke. A post-rehabilitation follow-up study. Stroke 1993;24: 200–205.

15 Unwin H, Walker-Batson D: No side effects after low-dose amphetamine administration in stroke rehabilitation. Stroke 2000;31:1788–1789.

16 Gladstone DJ, Black SA: Enhancing recovery after stroke with noradrenergic pharmacotherapy: A new frontier? Can J Neurol Sci 2000;27: 97–105.