Amphetamine Paired With Physical Therapy Accelerates Motor Recovery After Stroke

Further Evidence

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Background and Purpose In animal models of brain injury, administration of numerous pharmaceuticals is reported to facilitate functional recovery. However, only drugs that increase the release of norepinephrine have been shown to promote recovery when administered late (days to weeks) after injury. To determine whether these findings were applicable to humans, we administered the norepinephrine stimulant dextroamphetamine, paired with physical therapy, to hemiplegic stroke patients.

Methods Ten hemiplegic patients who suffered an acute ischemic infarction were entered between days 16 and 30 after onset and randomly assigned to receive either 10 mg of dextroamphetamine or a placebo orally every fourth day for 10 sessions paired with physical therapy. The Fugl-Meyer Motor Scale was used at baseline, within each session, and for 12 months after onset as the dependent measure. Confounding medications such as α-adrenergic antagonists or agonists were excluded in all subjects.

Results Although there were no differences between the groups at baseline ($P=.599$), there was a significant ($P=.047$) difference between the groups when the drug had been discontinued for 1 week and at the 12-month follow-up visit ($P=.047$).

Conclusions Administration of dextroamphetamine paired with physical therapy increased the rate and extent of motor recovery in a small group of hemiplegic stroke patients. These data support and extend previous findings of the facilitatory aspects of certain types of drugs on recovery from brain injury. The use of neuromodulation may allow the nervous system to adapt previously unused or alternative pathways to relevant external input. (***Stroke.* 1995;26:2254-2259.**)

Key Words • cerebrovascular disorders • hemiplegia • dextroamphetamine • stroke

Accumulating evidence over the past 20 years from the basic science laboratory has produced significant advances in knowledge regarding central nervous system plasticity and recovery of function,[1-3] yet there has been little application of this knowledge to neurological rehabilitation methodologies. It has been shown that after a permanent brain injury in which no significant regrowth of lost tissue occurs, behaviors that were lost initially exhibit some spontaneous recovery.[2] This behavioral change over time forms the theoretical foundation of contemporary theories of recovery of function after brain injury. Moreover, the observation of behavioral change clearly indicates that the remaining brain must have compensated on some recovery parameters when given at early or later time points after brain injury.[5-11] Changes in catecholaminergic, particularly norepinephrine, functioning after brain injury have been correlated with changes in the rate of recovery after injury. For example, a single dose of dextroamphetamine (AMPH) has been reported to produce an enduring acceleration of motor recovery after experimental lesions in the rat.[5] Multiple dosing, alternated every fourth day, has also accelerated motor recovery in the cat.[6] While this animal study reported generalized improvement with AMPH administration alone, the greatest improvement occurs when modality-specific training or testing is paired with drug administration.[5,6,11] Similar findings have been reported in the

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from aphasia after stroke in humans.[15] Thus, there is increasing evidence that AMPH administration may provide symptomatic management for some deficits after brain injury in humans

tion is limited. Davis and colleagues[19,20] reported that hemiplegic patients who received a single dose of AMPH administered 45 minutes before intensive physical therapy scored 40% better on a standardized motor scale than those on placebo. These patients were followed after AMPH administration for only 24 hours.

more recovery of speech and language deficits subsequent to stroke.[21,22] Our protocol, which we adapted from previous animal and human reports,[5,6,19] specifies that patients be entered between days 16 and 30 after onset and receive an oral dose of AMPH or a placebo every fourth day for 10 sessions, paired with modality-specific therapy. In the present investigation we studied the effect of administration of AMPH compared with a placebo on recovery from hemiplegia after ischemic stroke during 12 months after onset. The Fugl-Meyer Motor Scale[23] was chosen as the dependent measure of

Ten hemiplegic subjects (four men and six women) who had a single thromboembolic nonhemorrhagic infarction participated in the study. The presence of hemiplegia was defined as a score of 55 or lower on the Fugl-Meyer Motor Scale[23] at baseline screening. This careful subject definition of moderately severe (Fugl-Meyer score of 36 to 55) or severe (Fugl-Meyer score of 0 to 35) motor deficits was purposely established in an attempt for some control of severity across subjects. Subjects studied were between the ages of 48 and 73 years. Exclusion criteria specified that none of the subjects have a terminal medical condition such as AIDS or cancer, other coincident neurological disease, history of psychiatric illness or extensive alcohol or drug abuse, unstable cardiac dysrhythmia or hypertension not controlled by medication (160/100 mm Hg), or untreated hyperthyroidism. Additionally, they could not be receiving α-adrenergic antagonists or agonists, major or minor tranquilizers, or be older than 80 years. Documentation of all medications was kept on all subjects after the stroke to establish that at no time during the 12-month study period did any subject receive any confounding drugs. Complicating drugs included α-adrenergic antagonists or agonists as well as other agents such as neuroleptics, benzodiazepines, and antidepressants shown to affect behavioral recovery in laboratory animals[24,25] and motor recovery in humans.[26] Written informed consent was obtained from each subject before the study, and the research protocol was approved by the institutional review for human subjects at each of the participating medical centers.

Procedures

During the 3.5-year course of the study, the medical charts of approximately 400 patients were screened. The most frequently occurring reasons for patient exclusion were evidence of hemorrhagic or brain stem strokes, previous cerebral lesions with residual deficits, mild motor deficits, multiple medical problems, other coexisting neurological conditions, and age (see "Appendix" for an example of our chart review and exclusion documentation for a typical 3-month period). Those subjects meeting criteria for entry and who consented were assigned to either the AMPH or placebo group by a random drawing performed by the neuroscience nurse. To ensure patient safety, we chose to use a single-blind procedure in this initial study. The primary investigator (D.W.-B.), the investigator neurologists (R.G., H.U.), and the neuroscience nurse were unblinded. All other participants, including the patients, their physicians at the collaborating medical centers, and the physical therapists who provided the study evaluations and treatment, were blinded as to drug/placebo assignment. Subjects were entered between days 16 and 30 after onset of their stroke. Baseline motor scores on the Fugl-Meyer Motor Scale were obtained 1 day before study initiation in all subjects. Seven of the 10 was only 1 point.

Drug Administration and Physical Therapy Treatment

All subjects (with the exception of subject 4) received an oral dose of 10 mg AMPH or a placebo in capsule form every fourth day for 10 sessions. Subject 4 was the first patient studied on the motor component of our work, and she received a 15-mg dose for the first six sessions. Because she complained of difficulty sleeping, the dose was decreased to 10 mg for the remaining four sessions. Blood pressure and heart rate were monitored before and during each AMPH/placebo session. We carefully

attempted in each area addressed by the Fugl-Meyer Motor Scale: Upper extremity/Hand/Upper Extremity coordination and Lower extremity/Lower extremity coordination. Success and degree of difficulty of the attempted task in each section during each treatment session were documented. Patient failure on a specific task was not reason enough to omit the task from the program.

Data Analysis

The dependent measure was the Fugl-Meyer Motor Scale.[23] This measure has been shown to have high interobserver and intraobserver reliability.[28] The scale has a possible total motor score of 100, with a score greater than 93 considered to be in the normal range of function. Because of the ordinal nature of the scale, we used nonparametric statistics to analyze the data. Fugl-Meyer Motor Scale scores were obtained at baseline, during each AMPH/placebo session, 7 days after drug sessions stopped, and again at 3, 6, and 12 months after onset.

Results

Table 1 summarizes the day of study initiation, sex, age, neurological deficits, and radiological data for each of the 10 subjects studied. (Subject numbering reflects the fact that we study both hemiplegia and aphasia after stroke. Subjects are numbered consecutively whether they participated in the motor and/or language aspect of the protocol.) The mean day of initiation of the study was 23 days after onset for the AMPH group and 22 days after onset for the placebo group. The mean age was 61 years in the AMPH group and 67 years in the placebo group. The AMPH group was composed of 4 women and 1 man; the placebo group was composed of 2 women and 3 men. Four subjects in the AMPH group had left hemisphere infarction with co-occurring aphasia; 1 had right hemisphere infarction. One subject in the placebo group had left hemisphere infarction with co-occurring aphasia; 4 had right hemisphere infarction. Six of the 10 subjects had CT evidence of cortical and adjacent white matter involvement, 1 subject in the AMPH group had a large striatal infarct, 2 subjects in the placebo group had small lacunar infarcts, and 1 placebo subject had no evidence of infarct on CT. Within-session monitoring of

TABLE 1. Day of Study Initiation, Sex, Age, Neurological Information, and CT Data on Each Subject

Pt No. (Day Medicine Began)	Sex/Age, y	Neurological Deficits	CT Site
AMPH group			
4 (day 16)	F/48	Rt hemiplegia, AL; hemisensory	Large striatal infarct
9 (day 18)	M/50	Rt hemiplegia, AL; hemisensory, VF	MCA anterior cortical/subcortical
12 (day 30)	F/72	Rt hemiplegia, AL; hemisensory, VF	MCA anterior and posterior cortical/subcortical
17 (day 23)	F/73	Lt hemiplegia, AL; hemisensory, VF	MCA anterior and posterior cortical/subcortical
21 (day 30)	F/63	Rt hemiplegia, AL; hemisensory, VF	MCA cortical/subcortical
Placebo group			
16 (day 17)	F/67	Lt hemiplegia, AL	Lucunar stroke, small-vessel disease, posterior limb internal capsule
18 (day 30)	M/62	Rt Hemiplegia, AL; hemisensory	MCA anterior cortical/subcortical
19 (day 19)	M/68	Lt hemiplegia, AL; hemisensory, VF	MCA posterior cortical
20 (day 18)	F/71	Lt hemiplegia, AL; VF	Subcortical, anterior limb of internal capsule
22 (day 27)	M/71	Lt hemiplegia, AL; hemisensory	No evidence of infarct on CT

Pt indicates patient; AMPH, dextroamphetamine; Rt, right; A, arm; L, leg; VF, visual field; Lt, left; and MCA, middle cerebral artery.

heart rate and blood pressure revealed no significant fluctuations due to drug administration. In addition, at no time during the 12-month course of the study was there documentation of any negative event that could be attributed to AMPH administration.

There were no baseline differences on the motor scale between the two groups (Table 2). The baseline median Fugl-Meyer score was 19.5 in the AMPH group compared with 19 in the placebo group ($P=.599$, Mann-Whitney U test). At baseline, 9 of the 10 subjects studied had a score below 35 on the Fugl-Meyer Motor Scale, classifying these subjects in the severe range of motor deficits on the severity stratification suggested by Duncan et al.[29] Subject 17 had an initial score of 36, which is in the moderately severe range. Individual motor scores at baseline, during the 10 sessions, and when the drug had been discontinued for 1 week are shown in Table 2. Differences between the two groups began to emerge by session 2 and continued 1 week after drug administration and during 12 months after onset (Figure). Gain scores between baseline and 1 week after AMPH/placebo sessions and baseline and 12 months after onset were computed for each patient in each of the two groups. A two-tailed Mann-Whitney test was used to compare the differences from baseline to these two time periods in the gain scores of the two groups. The tests revealed a significant ($P=.047$) difference between the groups at both time periods, with greater motor improvement in the AMPH group.

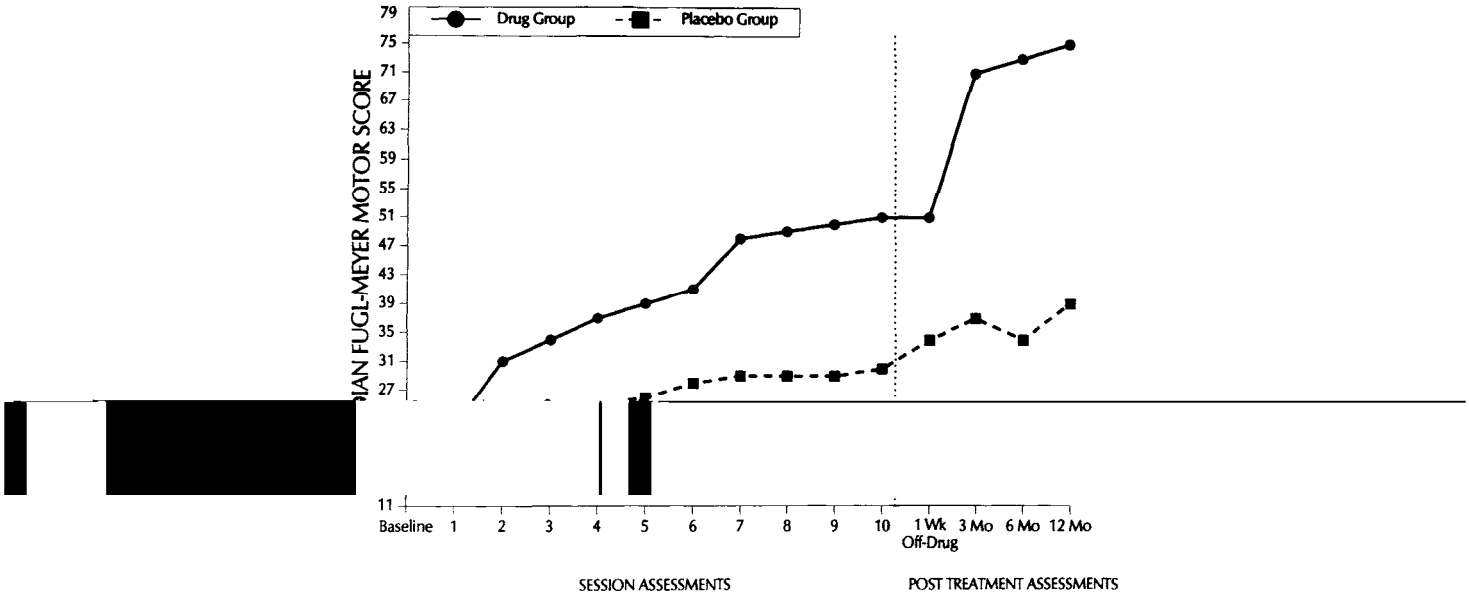
Discussion

In this study of 10 stroke subjects with severe motor deficits, administration of AMPH paired with intensive physical therapy during the subacute recovery period accelerated the rate and increased the final level of motor recovery as assessed by a standardized scale of

TABLE 2. Fugl-Meyer Motor Scale Scores of Each Subject and Group Median Scores From Baseline Through 1 Week After Treatment

		Session										
Pt No.	Base-line	1	2	3	4	5	6	7	8	9	10	1 Week Off Drug
AMPH group												
4	21	21	31	34	37	39	41	46	49	50	51	51
9	21	32	41	47	51	54	56	58	59	62	63	69
12	18	22	25	28	28	28	28	28	28	28	28	28
17	36	36	40	47	50	55	55	58	58	58	62	62
21	16	17	19	23	27	33	38	38	38	39	39	41
Median	19.5	22	31	34	37	39	41	48	49	50	51	51
Placebo group												
16	31	31	31	31	31	31	34	35	35	35	35	35
18	11	12	12	12	12	15	17	17	20	20	26	27
19	23	24	28	28	35	35	36	36	36	36	36	36
20	9	9	9	13	13	12	14	15	16	16	16	16
22	19	23	23	25	25	26	28	29	29	29	30	34
Median	19	23	23	25	25	26	28	29	29	29	30	34

Pt indicates patient; AMPH, dextroamphetamine.



Line graph shows median Fugl-Meyer Motor Scale scores at baseline, during the 10 sessions, when the drug had been discontinued for 1 week, and 3, 6, and 12 months after onset.

motor ability. The increase in motor recovery was significant 1 week after drug sessions were finished, and the level of this recovery was maintained at the 12-month follow-up. This confirms and extends previous reports of

[redacted]

ceived a single dose of AMPH compared with placebo when paired with physical therapy and followed for 24 hours. Subjects in the study of Davis et al were entered in the acute period after stroke (before day 10 after onset), whereas we entered subjects in the subacute period after stroke (between days 16 and 30 after onset). We administered either AMPH or placebo every fourth day for 10 sessions before intensive physical therapy, compared with a single dose in the Davis study.

In previous studies we reported an AMPH-enhanced recovery from aphasia after ischemic stroke[21,22] with the

[redacted]

period of drug action.[24] It is not clear whether this timing effort is important or whether other dosing or therapy scheduling protocols would be more or less efficacious. One recent study on AMPH administration in the treatment of hemiplegia used a continuous dosing schedule over 17 days and did not find a significant difference between AMPH and placebo patients.[30] This study, which also used the Fugl-Meyer Motor Scale, entered patients after day 30 and did not standardize the time interval after drug administration before physical therapy was initiated or the length or intensity of the therapy (S. Borucki, conversation, 1994).

The present results extend previous findings in several important ways. First, they indicate that the therapeutic window for using AMPH may extend up to 30 days after ictus. Second, multiple administrations appear to provide further therapeutic benefit to the patient (Figure). It cannot be determined from this study, however, exactly how many administrations of AMPH are needed for an optimal level of recovery. Since AMPH is a potent releaser of neurotransmitters, continuous administration would deplete the stores of the neurotransmitter system

[redacted]

return on therapeutic efficacy. In the present study we purposely spaced the oral administration of AMPH in an attempt to prevent tolerance effects to AMPH administration. Third, the effects of multiple oral administrations combined with physical therapy significantly maintained the level of motor recovery at 12 months after injury, long after the last oral administration of AMPH. This finding indicates that extremely protracted therapy with AMPH may not be necessary (or desirable) in the brain-injured patient.

The neural mechanisms for AMPH-enhanced re-

[redacted]

when AMPH administration is paired with tactile stimulation in rats 30 days after infarct, a correlated increase in metabolic activity has been found in regions surrounding the site of injury in somatosensory cortex.[32] These data have been interpreted to suggest that AMPH-mediated release of neuromodulators such as norepinephrine may provide a condition of increased cortical excitability that permits circuit modification in postinjury states when paired with task-specific practice or stimulation.[9,32] Other recent animal studies without pharmacological probes report an increase in synaptogenesis and sprouting from 14 to 60 days after cortical infarction.[33] Mechanisms of learning and memory could also occur in this time frame since AMPH as been shown to affect long-term potentiation.[34]

Our observations suggest that the subacute period after stroke may be an important window for AMPH

administration when paired with relevant therapies for restoration of function in humans. This study is limited because of the small select group of hemiplegic subjects and may not represent all stroke patients. However, because we studied only patients whose motor deficits were initially classified as severe,[26] effects in this small sample would appear to be meaningful. We believe that the results of this study suggest that the use of animal models employing pharmacological manipulations after brain injury may also have clinical correlates for stroke recovery in humans. Clinical trials involving greater numbers and greater varieties of patients appear warranted based on the present findings.

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Appendix

Chart Review Summary: March 1 to June 30, 1995

80 Number of charts reviewed
2 Number of potential research subjects
78 Number of exclusions

Reasons for Exclusion

18 Hemorrhagic or brain stem stroke
11 Multiple cerebral lesions with residual deficits
5 Greater than 30 days after stroke
0 Corrected vision no worse than 20/100 in at least one eye
15 Mild motor deficits
0 History of head injury with loss of consciousness
4 Terminal illness/confounding medical problems
9 Neurological condition other than stroke
1 History of alcohol or drug abuse (required treatment)
1 History of psychiatric illness
0 Inability to read or write before stroke
0 Lack of sensorimotor ability sufficient in one upper extremity to write or gesture
1 Unstable cardiac dysrhythmia or hypertension (160/100 mm Hg)
0 Untreated hyperthyroidism
0 Receiving α-adrenergic antagonist or agonists
1 Receiving major/minor tranquilizers, including clonidine, prazosin, γ-aminobutyric acid, benzodiazepine, scopolamine, haloperidol, neuroleptics such as trifluoperazine, fluoxetine hydrochloride, or other atypical psychological drugs

Note: The same exclusion criteria have been used throughout the study; however, documentation initially was not centralized from the various medical centers and is not now available for analysis.

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