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Nicotine Patches in Alzheimer's Disease: Pilot Study on Learning, Memory, and Safety

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WILSON, A. L., L. K. LANGLEY, J. MONLEY, T. BAUER, S. ROTTUNDA, E. McFALLS, C. KOVERA AND J. R. McCARTEN. *Nicotine patches in Alzheimer's disease: Pilot study on learning, memory, and safety.* PHARMACOL BIOCHEM BEHAV 51(2/3) 509–514, 1995.—In view of the cholinergic deficits present in patients with Alzheimer's disease (AD), a widely investigated treatment strategy for the cognitive deficits in AD is cholinergic stimulation. Although nicotinic cholinergic receptor binding has been demonstrated to be deficient in the AD brain, the predominant theoretical and therapeutic focus to date has been on muscarinic cholinergic receptors and systems. The purpose of the present study was to evaluate the effects of sustained nicotine administration on behavior, cognition, and physiology. A double-blind placebo-controlled trial was conducted in which six patients with probable AD were exposed to 7, 8, and 7 days of placebo, nicotine, and washout, respectively. Daily sessions evaluating learning, memory, and behavior were conducted. Global cognitive functioning, rest and activity levels, cardiac activity, and blood levels were also measured. Findings included improved learning during the nicotine condition, which persisted throughout washout. Memory, behavior, and global cognition were not significantly affected. Sustained administration of nicotine appeared to be safe, although sleep showed a significant decrease.

Alzheimer's disease Nicotine Learning Memory Delayed matching to sample Repeated acquisition
Behavior Cardiac Human Actigraph TimeWand

ALZHEIMER'S disease (AD), a degenerative brain disease and the leading cause of dementia in the elderly, is associated with a well-established deficit in brain acetylcholine. This cholinergic deficit has been the focus of many drug trials, and recently the acetylcholinesterase inhibitor tacrine was approved by the Food and Drug Administration for the symptomatic treatment of AD. Tacrine, like most other cholinergic agents tested, has been presumed to exert its effects primarily through the muscarinic cholinergic system. Little attention has been paid to the nicotinic cholinergic system, despite the demonstrated deficiency of nicotinic receptors in the AD brain. Research demonstrating the importance of nicotinic mechanisms in the treatment of AD is beginning to accumulate (18,19,20,22). Using positron emission tomography (PET), Nordberg et al. demonstrated that tacrine induces changes in AD brains consistent with restoration of nicotinic receptors (21,23).

The nicotinic system in the brain is fundamentally different from the muscarinic system. Postsynaptic nicotinic receptors are coupled to ion channels, whereas muscarinic receptors are G-protein coupled (29). Unlike muscarinic receptors, nicotinic receptors demonstrate upregulation with chronic stimulation (12). In addition to its postsynaptic effects, nicotine, the prototypical agonist of the nicotinic system, also stimulates the release of presynaptic acetylcholine, and has effects on several other transmitter systems, including dopamine, norepinephrine, serotonin, and GABA (9).

In rats, nicotine has been shown to improve memory and learning without evidence of tolerance over 3 weeks (9–11). In both young and aged monkeys, nicotine enhanced performance on delayed matching to sample (DMTS), a measure of short-term memory. Greatest improvement was seen at longer intervals of delay, and improvements persisted at both 10 min and 24 h after injection (2). In normal nonsmoking humans, simple motor responding (32), auditory and visual vigilance (30,31), and attention to relevant stimuli (28) improved following acute nicotine administration.

Only three published studies addressed the effects of nico-

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tine administration in AD patients, all of which investigated acute intravenous (IV) or SC administration. Significant dose-dependent improvements were reported in immediate free recall (17), reaction time (25), sustained visual attention, and perception (6), all of which are deficient in AD.

The current study is an initial assessment of the cognitive, behavioral, and physiologic effects of chronic nicotine delivered via transdermal patch.

METHOD

Subjects

Subjects were five men and one woman with probable AD according to DSM-III-R guidelines (1) and the NINCDS-ADRDA Work Group recommendations (15), chosen consecutively from the Geriatric Research, Education, and Clinical Center (GRECC) Memory Loss Clinic at the Minneapolis Department of Veterans Affairs Medical Center (VAMC), which consists predominantly of male patients. Subjects were 71–84 years old, with a mean age of 78.6. Mini-Mental State Examination (MMSE) (3) scores ranged from 14-22, with a mean of 19.5 of 30 possible points (higher scores indicate better performance), indicating dementia of mild to moderate severity. All had been nonsmokers for at least 8 years before the study and were in good general health. Informed consent was obtained from all subjects and their caregivers before enrollment.

Procedure

Subjects were admitted to the GRECC service intermediate care ward at the Minneapolis VAMC, given a general physical and neurologic examination, and allowed 2 or 3 days to acclimate to the setting. A within-subject A-B-A double-blind experimental design was employed in which subjects served as their own controls. Placebo or nicotine was administered via a transdermal patch applied daily for 7, 8, and 7 days during baseline, treatment, and washout, respectively. Because of the small number of subjects and the preliminary nature of the study, a decision was made to employ only one dosage level. We chose a patch containing 22 mg nicotine, the highest dosage available in commercial patches, delivering approximately 0.9 mg nicotine/h over a 24-h period. Previous reports of acute IV and SC administration of nicotine in AD patients have employed doses up to 0.5 μg/kg per 60 min. The current study employed an intermediate dose with regard to previous studies of nicotine administration in AD. Patches were placed on alternating back shoulder areas each morning promptly at 0830 h by nurses. All testing and procedures were conducted by individuals blinded to the experimental conditions, with the exception of actigraph and DMTS testing, which were conducted on computerized equipment.

DMTS. Drug effects on recent memory were evaluated using DMTS, well-established as a sensitive measure of drug effects (24). The test was fully computerized on a Macintosh II with a 13-inch color monitor and a Mac 'n Touch 2.2 touch screen (Apple Computer, Cupertino, CA). Sessions were held each morning between 1000 and 1030 h. Subjects matched a sample stimulus (a drawing of a familiar object) with one of four choice stimuli (various drawings of the same object), only one of which matched the sample exactly. Each sample stimulus appeared in the middle of the computer screen for at least 6 s. Touching the sample initiated a delay interval of variable length (screen dark), followed by a screen showing the four choices, each appearing in a separate quadrant of the screen. Recorded messages prompted the subject to touch the sample and the matching choice stimulus, and acknowledged correct choices. The position of the correct stimulus varied from trial to trial. The delay values for each subject, ranging from 1–120 s, were determined by preliminary testing to accommodate the ability of each subject. Four to five delay values that reflected several levels of performance (from 25–75% correct) were selected for each subject and were randomly presented an equal number of times over 32–40 trials each session.

Repeated acquisition. Drug effects on learning were evaluated using a repeated acquisition test, a procedure in which predetermined sequences of responding are reinforced, also known to be sensitive to drug effects (24). Each afternoon at 1530 h, subjects were seated at a table in front of a shallow box that held up to seven compartments, with three vertically arranged stimuli in each compartment. The experimenter lifted the lid over the first compartment (the first link in the chain) and instructed the subject to choose (point to) one of the three stimuli, either top (T), center (C), or bottom (B), one of which concealed a token. The experimenter picked up the stimulus indicated by the subject. If it did not have the token under it, the experimenter said, "No, that's not it," and the lid was closed for 8 s before returning to that link. If the subject made a correct choice, the experimenter said, "That's right, good job," and exposed the subject to the second link, and so forth, until a correct response had been made in each link of the response chain. This resulted in reinforcement for a sequence of responding such as T, T, C, B (four-link chain). When a correct choice was made in the final link (completion of a trial), subjects received a nickel. There was a 5-s ITI, and then the chain was repeated with the same response requirements. Each session consisted of 20 trials, and at the end of the session subjects were presented with an array of items (e.g., soda, chips, a dollar bill, a magazine) and were given the opportunity to exchange the nickels for the item of their choice. The correct response sequence was the same within each session, but changed from session to session and was random except that simple chains, such as T, B, T, B, were omitted; the same sequence was not correct two sessions in a row, and within a specified number of sessions each stimulus was correct the same number of times. The number of links in the chain, ranging from three to seven, was determined by preliminary testing in which successive links were added until a subject was performing within the range of 35–55% errors. The number of links remained constant for a given subject throughout the study.

Global cognitive functioning. Drug effects on global cognitive functioning were assessed using the Dementia Rating Scale (DRS) (14). The test was given weekly at 1300 h, on day 1 of baseline, day 1 of drug, day 8 of drug, and day 7 of washout.

Behavior observations. To investigate adverse or beneficial effects on behavior, data on 15 categories of behavior, including talking, engaging in task, walking, aggression, compliance, and repetitive and inappropriate behaviors, were collected using a portable bar-code recorder (TimeWand; Videx, Inc., Corvallis, OR) and downloaded onto a Macintosh SE (Cupertino, CA). Observation periods lasted 45 min and were conducted at 1615 h each weekday afternoon. (Operational definitions of each behavior are available upon request from the author.) Each observation period was divided into 135 20-s intervals. An unobtrusive observer watched the subject for 10 s and then marked one or more bar codes corresponding to the observed behavior over the next 10 s. Categories were not mutually exclu-

sive. Behaviors that occurred during the 10-s recording period were not scored. Interrater reliability was conducted twice for each subject. Agreement of two observers on the occurence of a behavior was computed for each of the 15 categories for each reliability session. Intervals with no occurences of behavior were not included in the analysis. Percent agreement was determined by dividing the number of agreements by the number of agreements plus disagreements × 100.

Activity monitoring. Rest and activity patterns were monitored with a portable wrist activity monitor, or actigraph (Ambulatory Monitoring, Inc., Ardsley, New York) worn continuously by subjects throughout the study. The actigraph uses a sensitive accelerometer to detect the presence of movements at a sampling frequency of 10 Hz. A bin size of 30 s allowed the recording and storage of movement data for consecutive 30-s intervals over 8 days. Available software generated estimates of sleep duration and distribution.

Cardiac monitoring. Drug effects on cardiac rate, rhythm, and ischemic changes were evaluated with Holter monitoring (Marquette Electronics, Inc., Jupiter, FL) conducted once during placebo and again during active drug.

Blood levels. Blood levels of nicotine and its active metabolite, cotinine, were taken at 3 and 24 h after application of the first two active patches, the last active patch, the first washout (placebo) patch, and on day 7 of washout. All blood level analyses were performed by Mayo Laboratories (Rochester, MN). Plasma nicotine and cotinine were measured using high performance liquid chromatography and ultraviolet detection. The lower limit of the nicotine assay was 2 ng/ml.

Statistical analysis. Repeated measures analysis of variance was used to analyze differences in percent correct on DMTS for each subject × session across conditions, repeated acquisition percent error × bin across conditions, behavior change × percent occurrence of each behavior for each subject across conditions, and global cognitive functioning × subject and category across conditions. Sleep data were analyzed using the nonparametric Wilcoxen Signed Ranks test.

RESULTS

Four of six patients showed improvement on repeated acquisition during the nicotine condition. Mean total errors for all six subjects were 43.1% during baseline, 35.9% during nicotine, and 36.2% during washout. Group data demonstrated a significant decrease in learning errors during nicotine administration compared to baseline [$F(2, 6) = 9.953$; $p < 0.05$], which remained low during washout (Fig. 1).

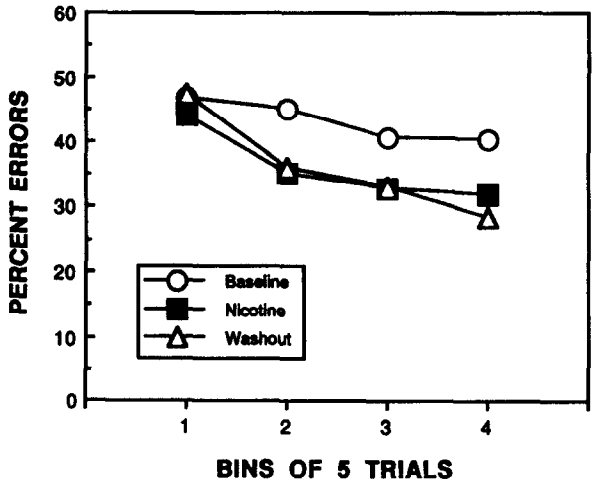

FIG. 1. Mean percent errors during baseline, nicotine, and washout conditions on repeated acquisition for six patients with probable Alzheimer's disease.

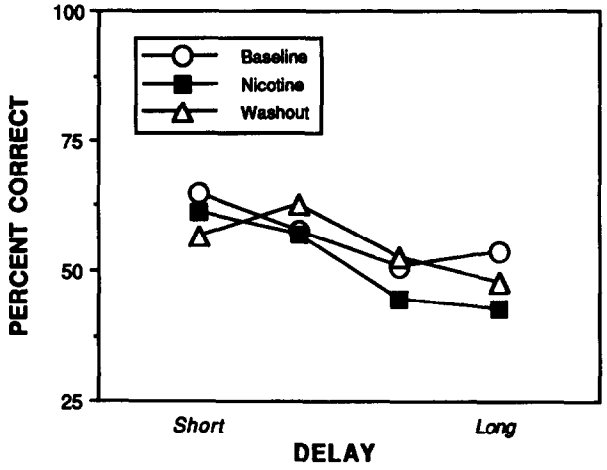

FIG. 2. Mean percent correct during baseline, nicotine, and washout conditions on delayed matching to sample for six patients with probable Alzheimer's disease. Chance level of responding is 25% correct.

Following nicotine administration, two of the subjects were noncompliant and left early or refused to come to several sessions during the nicotine and washout conditions. Repeated acquisition and behavioral observation data are based on data for completed sessions only

One patient showed improvement on DMTS during nicotine administration, but group DMTS performance was not significantly affected by nicotine in either direction (Fig. 2).

No patients showed significant change between any conditions on overall cognitive performance as measured by the DRS.

Behavior observations revealed no consistent changes between baseline, nicotine, and washout conditions, with the exception of on-task behavior defined as "engaging in a self-initiated, nonperseverative, appropriate activity with an apparent end, including self-care tasks, cleaning, watching TV, reading, writing a letter, arts and crafts, or other structured leisure activities, not including compliance to commands." Although not statistically significant, percent of time engaged in on-task behavior increased by a mean of 14.0% in five of six subjects during nicotine administration. Interobserver agreement for the behavior observations ranged from 51.1–96.4%, with a mean of 79.0%.

Activity monitoring revealed a significant decrease in sleep at night during nicotine administration. For the five subjects with actigraph data, the number of hours spent asleep from 2100–0700 h decreased from a baseline mean of 6.00 h (±0.78 h SE) to 5.00 h (±1.03 h SE) during drug treatment ($p < 0.05$). Compared to the drug condition, washout revealed a nonsignificant increase in sleep at night to a mean of 5.47 h (±0.99 h SE). The amount of daytime sleep was not affected by nicotine administration.

Three subjects dismantled or removed their Holter monitors before adequate data could be recorded. Of the three subjects who tolerated Holter monitoring for 24–48 continuous hours, all had mild increases in heart rate, with a 24-h

average increase of 5 beats/min (range 2--6). There were also mild increases in ectopy (heart beats occurring outside of the normal pathway of conduction), with ventricular ectopics increasing from an average of 0.40–0.54% of QRS complexes (the largest individual increase from 1.15 to 1.53%) and supraventricular ectopics increasing from 0.66 to 1.93% (the largest individual increase from 1.69 to 5.31%). There were no significant signs of ischemia.

Absorption of nicotine from the 22-mg patch was variable between subjects, with a range of peak blood levels from 3.9–11.7 ng/ml. A steady state of nicotine and cotinine was achieved in each patient, and by 48 h after removal of the patch no measurable amounts of nicotine or cotinine were in the blood (Fig. 3). Side-effects were infrequent and mild.

DISCUSSION

To our knowledge, this study constitutes the first attempt to investigate the effects of sustained transdermal delivery of nicotine in AD patients. Nicotine administration improved performance on a learning task (repeated acquisition) and was well tolerated with minimal side-effects and no significant cardiac toxicity. A steady state of nicotine and cotinine blood levels was achieved, which has not been previously investigated in an elderly or demented population.

The effects of nicotine on learning in patients with AD have not been previously reported. However, Newhouse et al. (17,33) reported impaired learning as measured by repeated acquisition following the administration of a nicotinic antagonist, mecamylamine, in normal humans. Subjects would appear to acquire the chain, but then "forget" and make an error. Interestingly, we observed the same pattern of errors in AD patients on repeated acquisition before nicotine administration.

The persistence of nicotine's effects on cognitive performance, such as the improvements on repeated acquisition that were maintained during washout, has been reported elsewhere. Levin and Rose (11) and Levin et al. (10) found improvements in radial-arm maze accuracy in rats at least 2 weeks after withdrawal of chronic nicotine administration. Even when rats were not pretested or tested during nicotine administration, performance by the nicotine group was superior to controls 4 weeks after nicotine withdrawal. Similarly, Buccafusco and Jackson (2 found, after an extended baseline period, reported improvements in monkeys at both 10 min and 24 h after IV nicotine administration, despite a 2-h half-life for nicotine. A possible mechanism for this effect is the upregulation of nicotinic receptors, which, in both humans and nonhumans, has been shown to occur in several brain regions including the cortex and striatum (7,8,12,13,26,27).

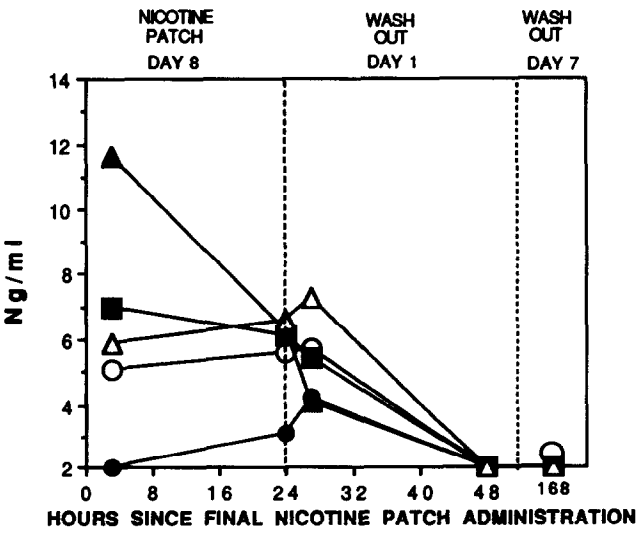

FIG. 3. Blood levels of nicotine on the final day of patch administration, the 1st day of washout, and after 7 days of washout for five of six patients. Blood was drawn twice for each patch: once at 3 h after patch application and once at 24 h after patch application (immediately preceding application of a new patch). The lowest level of detection was 2 ng/ml.

The lack of effect of nicotine on short-term memory in AD was also reported by Sahakian et al. (25). Although Newhouse et al. (17) found improvements in AD patients in a short-term recall task, the measured improvement was a decrease in intrusion errors from a distractor task. The length of time that a word could be remembered or an increase in the number of words remembered would be a more comparable measure to the DMTS task used in the present study. The current results add strength to the conclusion that nicotine does not improve recent memory in AD patients.

Our data also support conclusions that nicotine does not improve global cognition; however, a limitation of the clincial measure of utility (DRS) used in the present study is that the instrument is not validated as sensitive to changes induced by drugs. Practice effects prohibit more frequent testing; therefore, drug effects were evaluated based on only one sample per person.

Subjects tolerated 22 mg daily administration of nicotine with infrequent and mild side-effects. Nicotine may affect the cardiovascular system by a number of means, including increasing systolic and diastolic blood pressures, heart rate, and the force of myocardial contractions (4). Elderly patients, such as most patients with Alzheimer's disease, have a high incidence of coronary artery disease and may be at increased risk for cardiovascular complications from nicotine. Cardiac ischemia may be particularly dangerous in demented patients who may not reliably report symptoms. In those subjects who tolerated Holter monitoring, only mild changes in heart rate and ectopy and no significant ischemic changes were evident. Some subjects did report a vague feeling of lightheadedness, but no clinical change was apparent. Despite the relatively high dose of nicotine (the highest dose available in patch form), none of the patients, all of whom were nonsmokers for at least 8 years, reported or evidenced any sign of nausea.

Although behavioral observations revealed no significant changes, two of the subjects refused to attend several testing sessions during nicotine administration, in a belligerent and noncompliant manner. Newhouse (17) reported significant increases in anxiety and depression following nicotine administration, which may be consistent with the noncompliance we observed. A mood scale administered to the subjects did not produce valid data, probably because of subjects' impaired comprehension.

A potential behavior problem related to nicotine use is decreased nighttime sleep as measured by activity monitoring. Increased nighttime activity by AD patients puts a major strain on caregivers and is among the leading causes of nursing home placement (16). Although the effects of nicotine on sleep may be transient, such potential behavioral complications must be considered in drugs that would be used to treat the

cardinal symptoms of AD, memory and cognitive dysfunction.

In the present study, most of the behaviors targeted for observation occurred at a very low rate, possibly because the inpatient ward limited the opportunity for subjects to engage in activities representative of their normal behavior. Observation periods were held for only 45 min/day, and significant drug-related changes in behavior may have been missed. Extended observations in the home setting might reveal nicotine-related behavior changes not detected in the present study; however, no pronounced adverse behavioral changes were observed. Moreover, behavior observations revealed increases in self-initiated appropriate activity in five of six patients during nicotine administration.

The physiologic data from this study suggest that prolonged administration of nicotine delivered via transdermal patch is metabolized effectively and is probably safe in elderly AD patients. Repeated acquisition data support findings from other studies that suggest that nicotinic stimulation may enhance learning. Determination of dose-response relationships is important in future studies in AD patients, as animals studies indicate that the dose of nicotine is critical to performance and there is pronounced individual variability (5). Potentially adverse effects of nicotine on sleep and behavior in AD must also be considered.

In summary, the use of nicotine patches provides a probe to investigate nicotinic mechanisms in AD, appears to be safe for extended administration, and as a cholinergic replacement therapy, may provide some symptomatic benefit to AD patients.

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